LA ENFERMEDAD DE ALZHEIMER: UN TRANSTORNO METABOLICO

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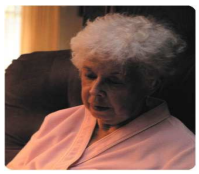
ciberned
Centro Investigación Biomédica en Red
Enfermedades Neurodegenerativas

UNIVERSITAT DE BARCELONA

¿ Que es la Enfermedad de Alzheimer?

La enfermedad de Alzheimer es la forma de demencia más común y es actualmente en los paises desarrollados un problema sanitario muy importante despues de enfermedades cardiovasculares y el cáncer.



- Es una enfermedad neurodegenerativa progresiva.
- Afecta el comportamiento del paciente, el aprendizaje y la habilidad de realizar las actividades de la vida diaria, provocando una perdida de independencia.
- Es <u>incurable</u> provocando la muerte del paciente.

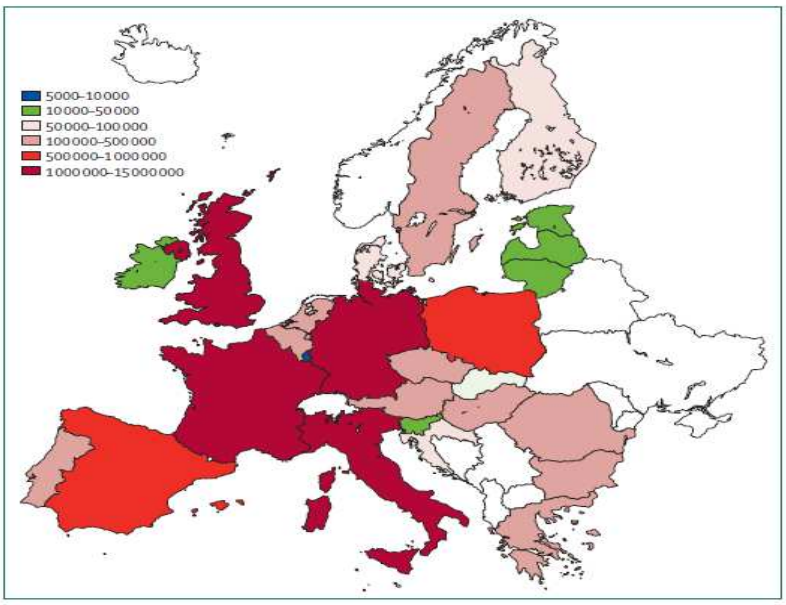


Figure 1: **Number of people with dementia in 28 European countries in 2013**
Estimates of the total number of people with dementia in each of 28 European countries were obtained from Alzheimer Europe [26]

ALOIS ALZHEIMER

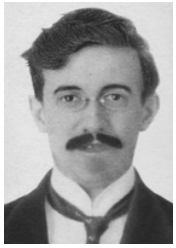
- Medico Alemán
- Hospital Mental observó a Augusta durante 5 años
- La autopsia reveló (1906) alteraciones en el cerebro

AUGUSTA D.

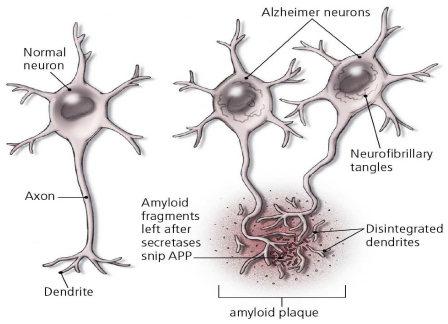
(Left to right) A. Alzheimer, E. Kraepelin, R. Gaupp, and F. Nissl. About 1906.

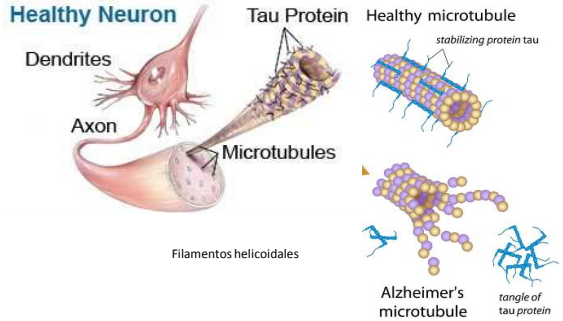
Alzheimer's modern histopathological laboratory in the Psychiatric University Hospital in Munich, 1904.

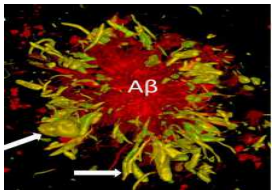
Alzheimer and coworkers in Munich. Back (left to right): F. Lotmar; unknown; St Rosental; Allers (?); unknown; A. Alzheimer; N. Achucarro, F. H. Levy. Front (left to right): Frau Grombach; U. Cerletti; unknown; F. Bonfiglio; G. Perusini. About 1909.

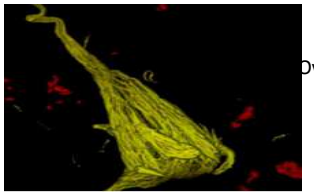


N. Achucarro Doctor honoris causa por la Universidad de Yale



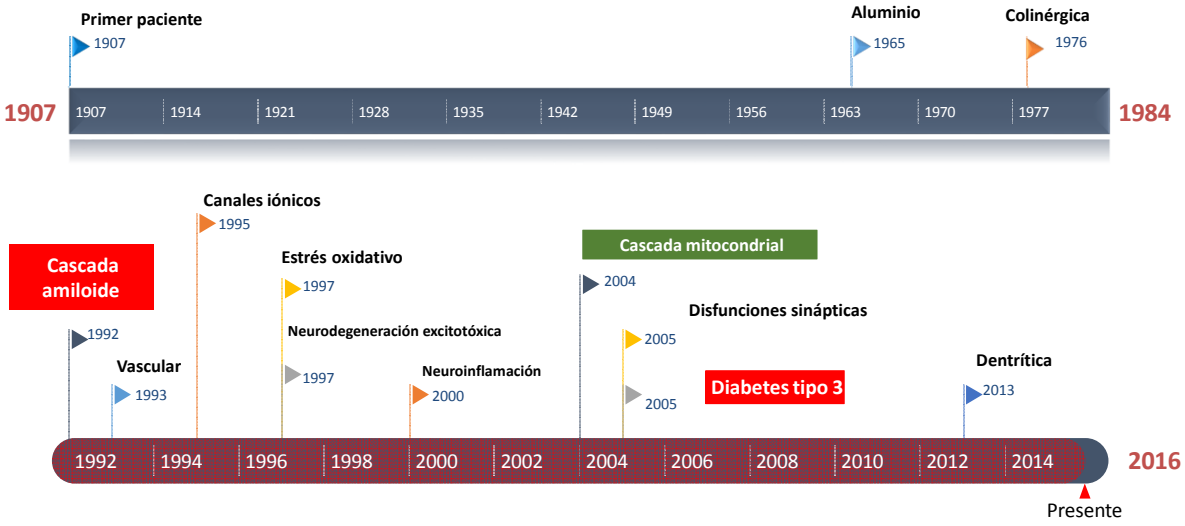






Ovillo neurofibrilar

Luna-Muñoz, J. & Harrington, C., 2013. Phosphorylation of Tau Protein Associated as a Protective Mechanism in the Presence of Toxic, C-Terminally Truncated Tau in Alzheimer's Disease. *Understanding Alzheimer's Disease*, p.89.



Adaptación de Petrov D., 2015. Efecto de una dieta rica en grasas en ratones app/ps1, modelo familiar de la enfermedad de Alzheimer.

The amyloid hypothesis of Alzheimer's disease at 25 years

Dennis J Selkoe[1,†] & John Hardy[2,*,†]

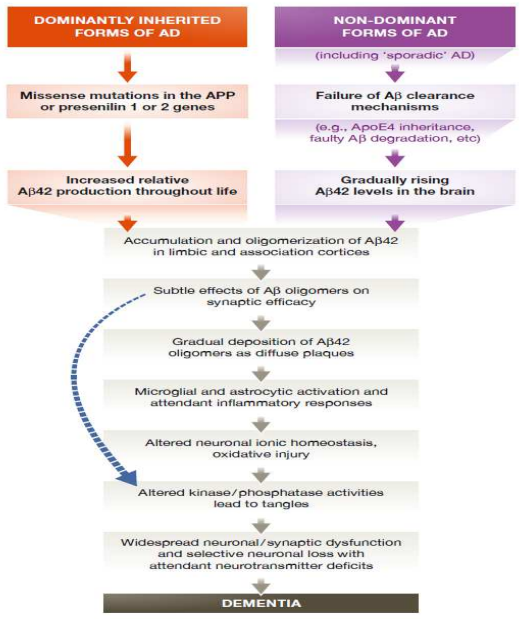
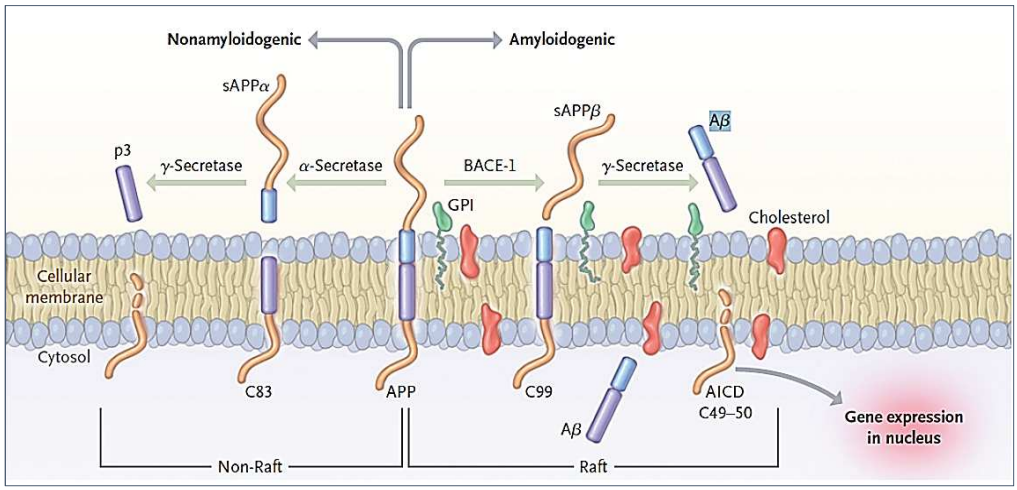


Figure 1. The sequence of major pathogenic events leading to AD proposed by the amyloid cascade hypothesis.
The curved blue arrow indicates that Aβ oligomers may directly injure the synapses and neurites of brain neurons, in addition to activating microglia and astrocytes.



Querfurth, H.W. & Laferla, F.M., 2010. Alzheimer's Disease. , 9, pp.329–344.

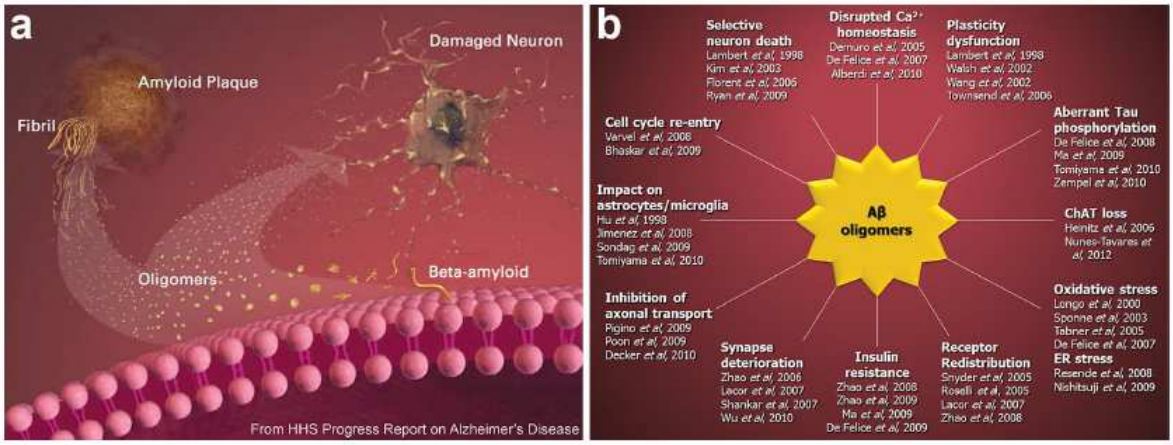
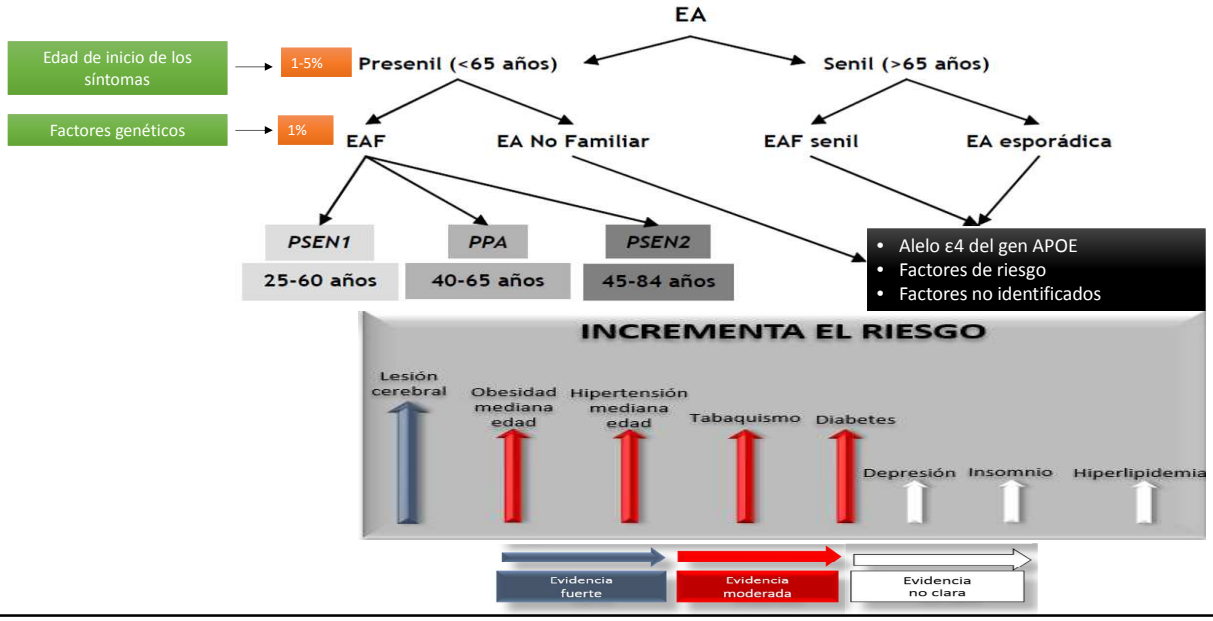
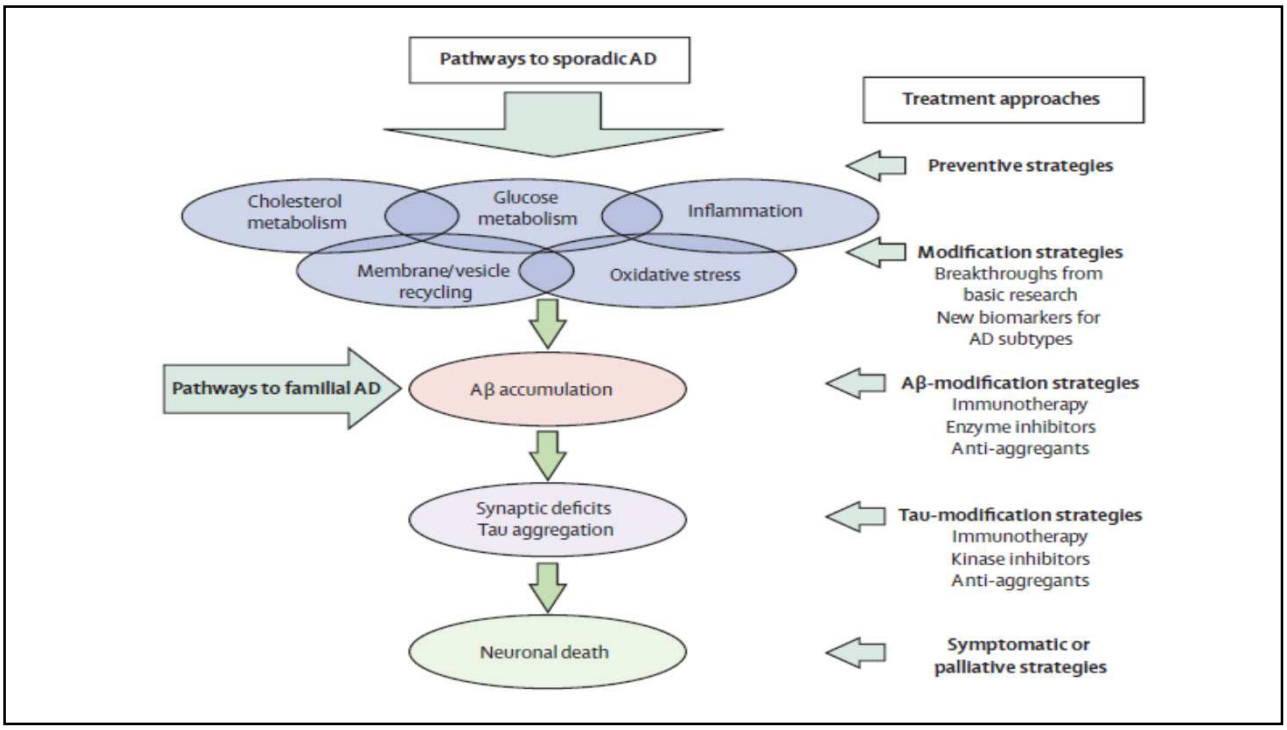
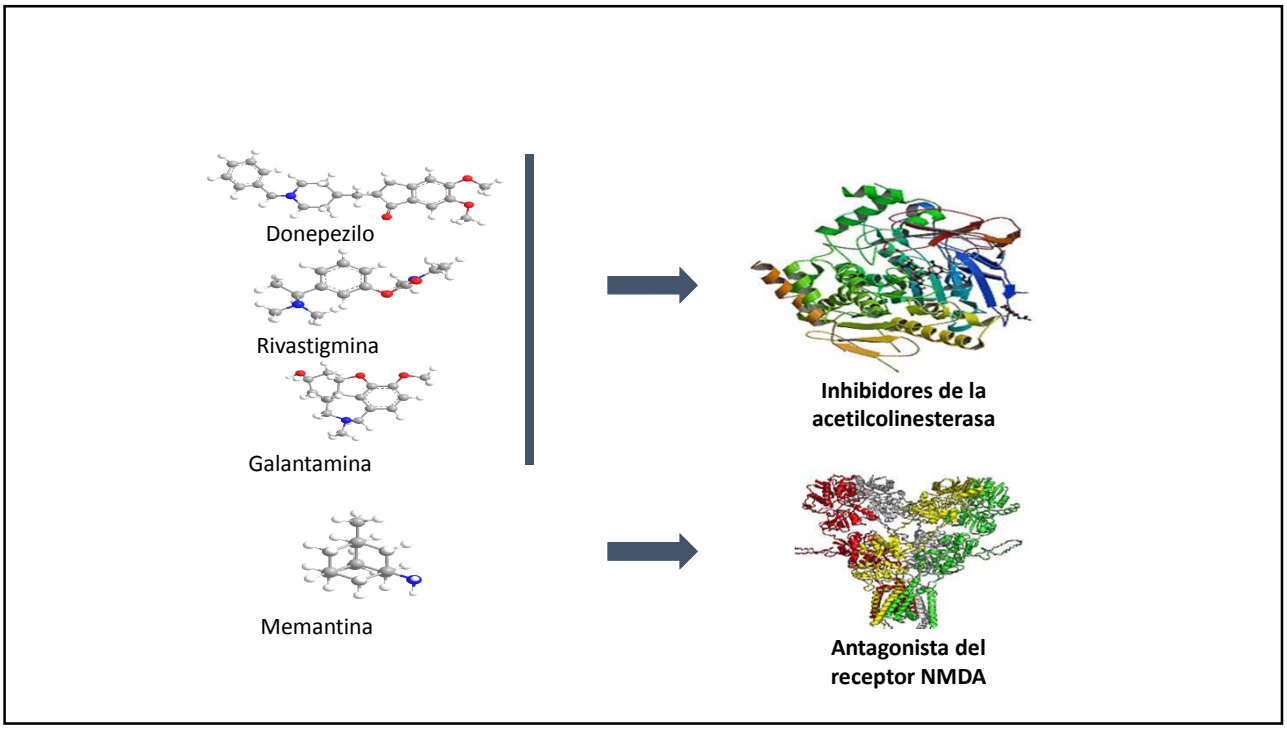


Fig. 1 Aβ oligomers (AβOs) instigate neuron damage in Alzheimer's disease. **a** Oligomeric Aβ, rather than insoluble amyloid species, instigates neuron damage in AD (adapted from the "2004/2005 Progress Report on Alzheimer's disease" Health and Human Services). **b** AD-associated changes attributed to AβOs

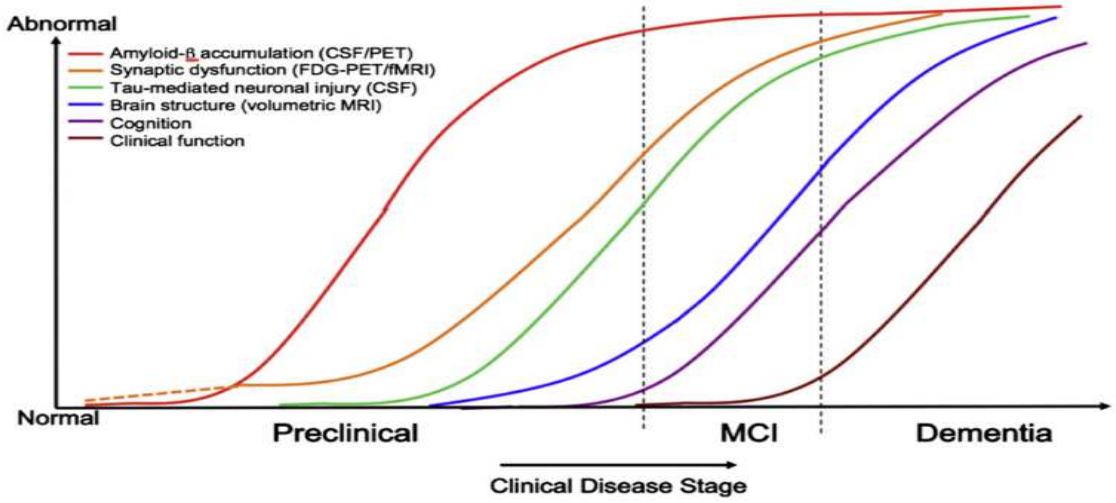



Pathways to sporadic AD
Treatment approaches
Preventive strategies
Cholesterol metabolism
Glucose metabolism
Inflammation
Membrane/vesicle recycling
Oxidative stress
Modification strategies
Breakthroughs from basic research
New biomarkers for AD subtypes
Pathways to familial AD
Aβ accumulation
Aβ-modification strategies
Immunotherapy
Enzyme inhibitors
Anti-aggregants
Synaptic deficits
Tau aggregation
Tau-modification strategies
Immunotherapy
Kinase inhibitors
Anti-aggregants
Neuronal death
Symptomatic or palliative strategies

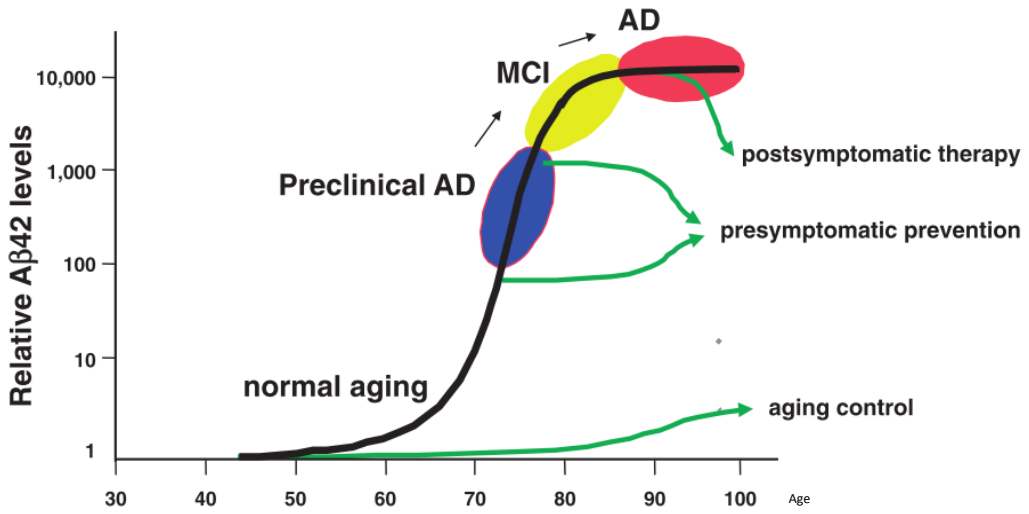

Donepezilo
Rivastigmina
Galantamina
Memantina
Inhibidores de la acetilcolinesterasa
Antagonista del receptor NMDA

NOMBRE DEL MEDICAMENTO	TIPO DE MEDICAMENTO Y USO
Aricept® **(donepezilo)** Previene la descomposición de la acetilcolina en el cerebro.	Inhibidor de colinesterasa recetado para el tratamiento de los síntomas de grado leve, moderado, y severo de la enfermedad de Alzheimer.
Exelon® **(rivastigmina)** Previene la descomposición de la acetilcolina en el cerebro y de la butirilcolina (un compuesto químico del cerebro similar a la acetilcolina).	Inhibidor de colinesterasa recetado para el tratamiento de los síntomas de grado leve a moderado de la enfermedad de Alzheimer. (El parche también es para casos de grado severo).
Razadyne® **(galantamina)** Previene la descomposición de la acetilcolina y estimula la liberación de niveles más altos de acetilcolina en el cerebro por los receptores nicotínicos.	Inhibidor de colinesterasa recetado para el tratamiento de los síntomas de grado leve a moderado de la enfermedad de Alzheimer.
Namenda® **(memantina)** Bloquea los efectos tóxicos asociados con el exceso de glutamato y regula la activación del glutamato.	Antagonista del N-metil D-aspartato (NMDA) recetado para el tratamiento de los síntomas de grado moderado a severo de la enfermedad de Alzheimer.

Medications, D., 2015. Alzheimer ' s Disease Medications. National Institute on Aging (NIH)
Calcoen, D., Elias, L. & Yu, X., 2015. What does it take to produce a breakthrough drug? *Nature reviews. Drug discovery*, 14(3), pp.161–2.



Sperling, R. a. et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3), pp.280–292.



Adaptation, Baumgart, M. et al., 2015. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 11(6), pp.1–9.

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

EXPERT REVIEWS

Masitinib for the treatment of mild to moderate Alzheimer's disease

Expert Rev. Neurother. Early online, 1–10 (2015)

Jaume Folch[1], Dmitry Petrov[2], Miren Ettecho[2], Ignacio Pedrós[1], Sonia Abad[2], Carlos Beas-Zarate[3,4], Alberto Lazarowski[5], Miguel Marin[6], Jordi Olloquequi[7], Carme Auladell[8] and Antoni Camins*[2,6]

[1]*Unitat de Bioquimica i Biotecnologia, Facultat de Medicina i Ciències de la*

Alzheimer's disease (AD) is a degenerative neurological disorder that is the most common cause of dementia and disability in older patients. Available treatments are symptomatic in nature and are only sufficient to improve the quality of life of AD patients temporarily. A potential strategy, currently under investigation, is to target cell-signaling pathways associated with neurodegeneration, in order to decrease neuroinflammation, excitotoxicity, and to improve cognitive functions. Current review centers on the role of neuroinflammation and the specific contribution of mast cells to AD pathophysiology. The authors look at masitinib therapy and the evidence presented through preclinical and clinical trials. Dual actions of masitinib as an inhibitor of mast cell–glia axis and a Fyn kinase blocker are discussed in the context of AD pathology. Masitinib is in Phase III clinical trials for the treatment of malignant melanoma, mastocytosis, multiple myeloma, gastrointestinal cancer and pancreatic cancer. It is also in Phase II/III clinical trials for the treatment of multiple sclerosis, rheumatoid arthritis and AD. Additional research is warranted to better investigate the potential effects of masitinib in combination with other drugs employed in AD treatment.

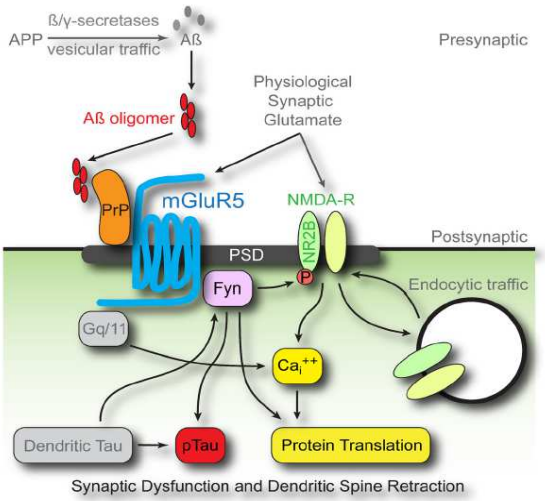


Figure 1 mGluR5 couples amyloid-beta oligomer–cellular prion protein to post-synaptic signaling. Schematic illustrating a central role of Fyn in amyloid-beta oligomer (Aβo) signaling. Binding of Aβo to cellular prion protein (PrP^C) triggers mGluR5-dependent signaling events. Proteins are clustered in the post-synaptic density (PSD) and alter *N*-methyl-D-aspartate receptor (NMDA-R) function, calcium and protein translation. Tau plays a role in localizing Fyn and is a Fyn substrate. The net result of aberrant PrP^C–mGluR5–Fyn signaling is synaptic malfunction and loss. Aβ, amyloid-beta; APP, amyloid precursor protein; PrP, prion protein.

Biochimica et Biophysica Acta 1842 (2014) 1556–1566

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Early alterations in energy metabolism in the hippocampus of APPswe/PS1dE9 mouse model of Alzheimer's disease

Ignacio Pedrós [b,c,h,1], Dmitry Petrov [a,c,h,1], Michael Allgaier [a,c,h], Francesc Sureda [b,c,h], Emma Barroso [a,d,h], Carlos Beas-Zarate [f,g,h], Carme Auladell [e,h], Mercè Pallàs [a,c,h], Manuel Vázquez-Carrera [a,d,h], Gemma Casadesús [f,h], Jaume Folch [b,c,h,2], Antoni Camins [a,c,h,*,2]

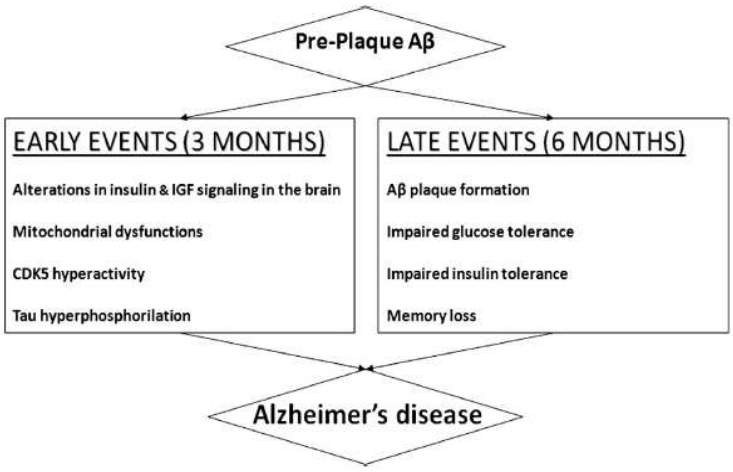
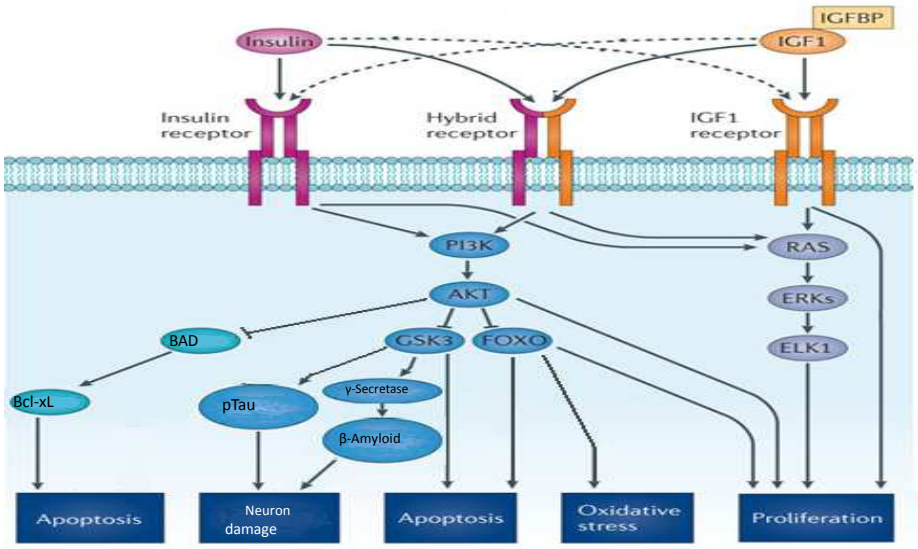


Fig. 9. Summary of the events, leading to the progressive amyloid plaque deposition and memory loss in an APP/PS1 mouse model of FAD.

SEÑALIZACIÓN DE LA INSULINA



IDE

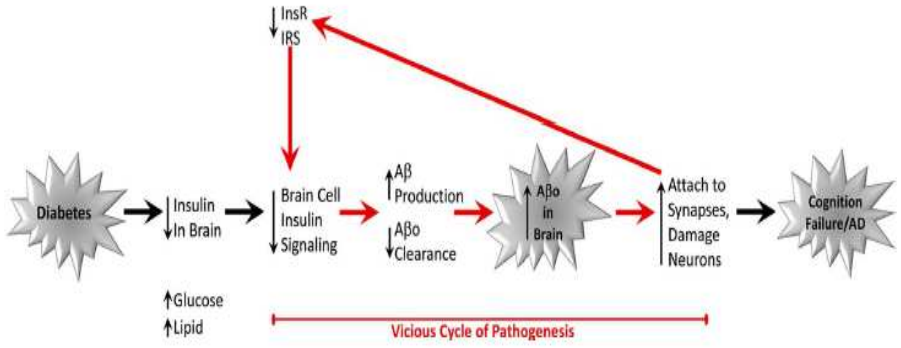


Fig. 3 Dysfunctional insulin signaling induced by AβOs provides one link to AD etiology. Diabetes causes a reduction in brain insulin and brain insulin signaling as well as an increase in glucose and lipids. This leads to an increase in Aβ production and a reduction in AβO clearance, causing a buildup of oligomers in the brain. As AβO levels rise, they bind synapses and cause neuronal damage, resulting in a decrease in insulin receptors and further reducing insulin signaling in brain cells. This vicious cycle results in cognitive failure and AD

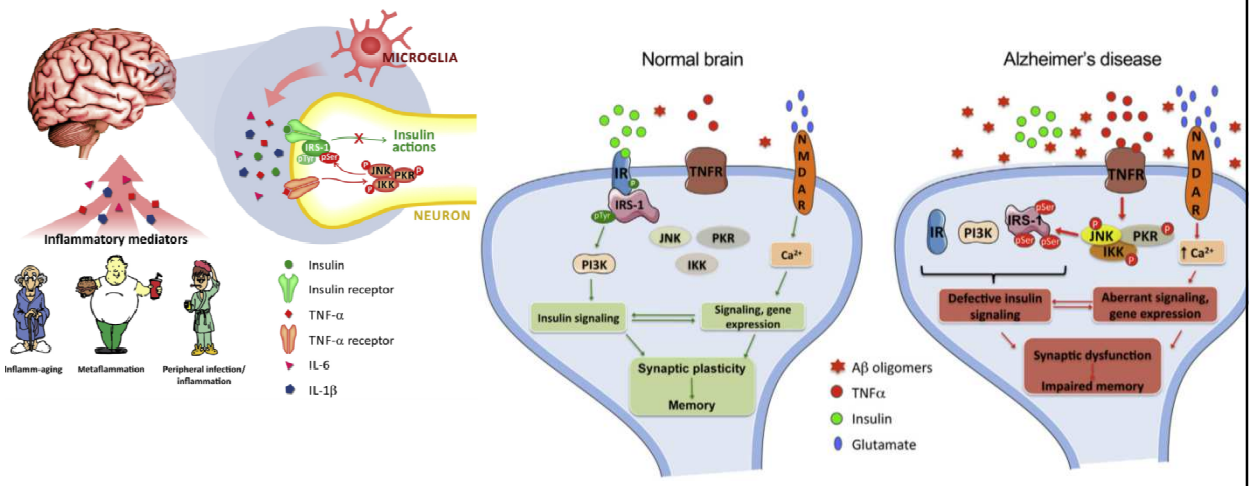
Hippocampal Insulin Resistance Impairs Spatial Learning and Synaptic Plasticity Diabetes 2015;64:3927–3936 | DOI: 10.2337/db15-0596

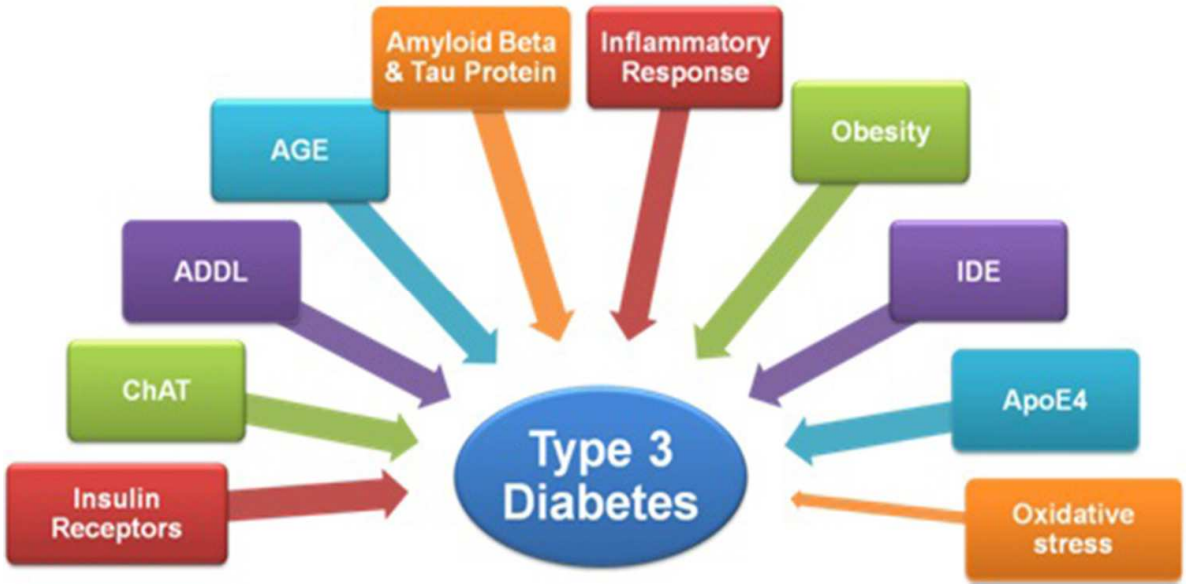
A Key Role of Insulin Receptors in Memory

Diabetes 2015;64:3653–3655 | DOI: 10.2337/dbi15-0011

To elucidate the functional role of hippocampal IRs independent of metabolic function, we generated a model of hippocampal-specific insulin resistance using a lentiviral vector expressing an IR antisense sequence (LV-IRAS). LV-IRAS effectively downregulates IR expression in the rat hippocampus without affecting body weight, adiposity, or peripheral glucose homeostasis.

How does brain insulin resistance develop in Alzheimer's disease?



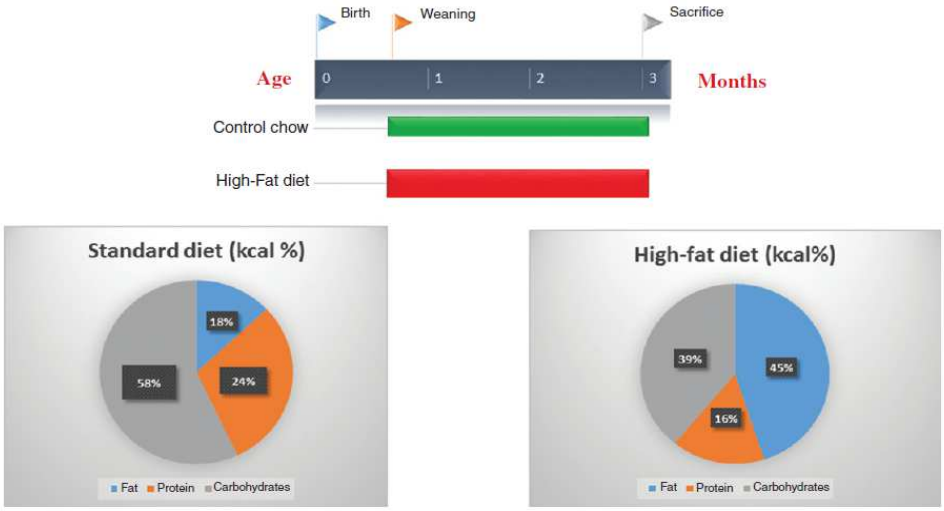


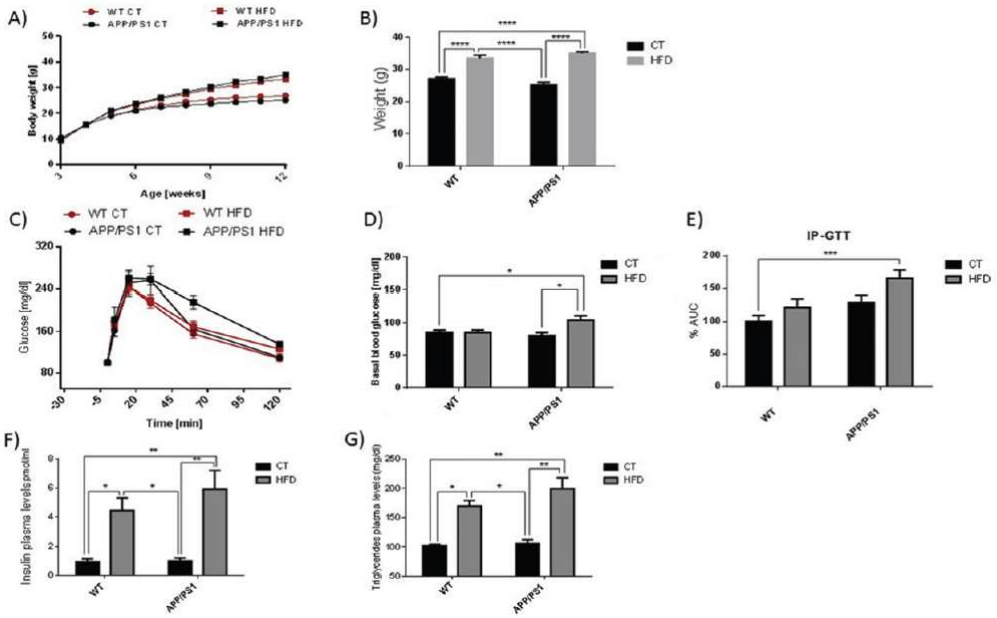
Journal of Alzheimer's Disease 54 (2016) 233–251
DOI 10.3233/JAD-160150
IOS Press

Evaluation of Neuropathological Effects of a High-Fat Diet in a Presymptomatic Alzheimer's Disease Stage in APP/PS1 Mice

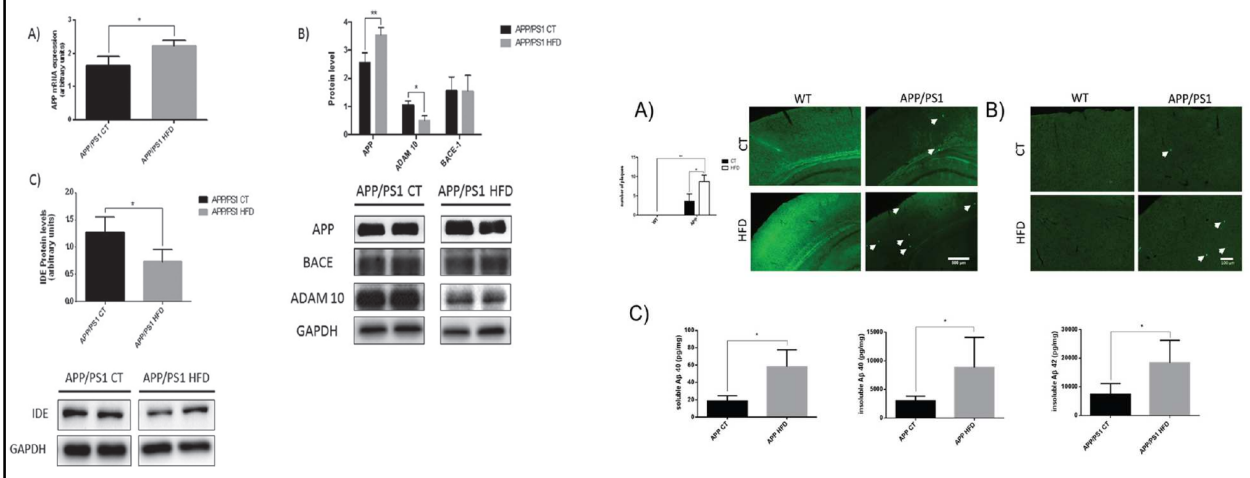
Miren Ettcheto[a,c], Dmitry Petrov[a,c], Ignacio Pedrós[b,c], Norma Alva[d], Teresa Carbonell[d], Carlos Beas-Zarate[f,g], Merce Pallas[a,c], Carme Auladell[e], Jaume Folch[b,c,1] and Antoni Camins[a,c,1,*]
[a]*Unitat de Farmacologia i Farmacognòsia, Institut de Neurociencias, Facultat de Farmàcia, Universitat de Barcelona, Barcelona, Spain*
[b]*Unitats de Bioquímica i Farmacologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus (Tarragona), Spain*
[c]*Biomedical Research Networking Center in Neurodegenerative Diseases (CIBERNED), Madrid, Spain*

EXPERIMENTAL SETUP





M. Ettcheto et al. / Evaluation of Effects of a High-Fat Diet in APP/PS1 Mice



M. Ettcheto et al. / Evaluation of Effects of a High-Fat Diet in APP/PS1 Mice

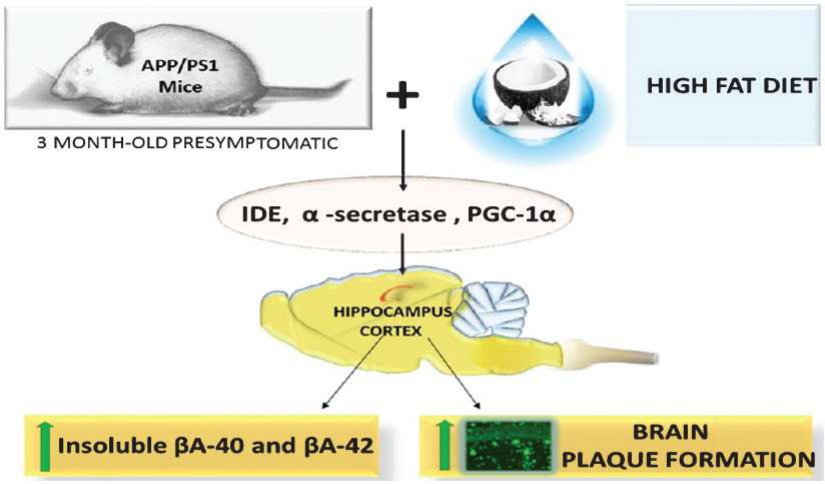


Fig. 12. A proposed mechanism whereby a HFD could elevate Aβ levels and plaque formation in brain APP/PS1 mice. HFD causes a reduction in three key molecules, PGC1α, IDE, and the α-secretase enzyme, which are directly involved in the production and metabolism of Aβ. These three proteins may constitute an early target for the treatment of AD in a presymptomatic stage.

M. Ettcheto et al. / Evaluation of Effects of a High-Fat Diet in APP/PS1 Mice

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Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

High-fat diet-induced deregulation of hippocampal insulin signaling and mitochondrial homeostasis deficiences contribute to Alzheimer disease pathology in rodents

Dmitry Petrov [a,c,1], Ignacio Pedrós [b,c,1], Gonzalo Artiach [a,c], Francesc X. Sureda [b,c], Emma Barroso [a,d], Mercè Pallàs [a,c], Gemma Casadesús [e], Carlos Beas-Zarate [f,g], Eva Carro [h], Isidro Ferrer [i], Manuel Vazquez-Carrera [a,d], Jaume Folch [b,c,2], Antoni Camins [a,c,j,*,2]

[a] Unitat de Farmacologia i Farmacognòsia, Facultat de Farmàcia, Institut de Biomedicina de la UB (IBUB), Universitat de Barcelona, Barcelona, Spain
[b] Unitats de Bioquímica i Farmacologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus (Tarragona), Spain
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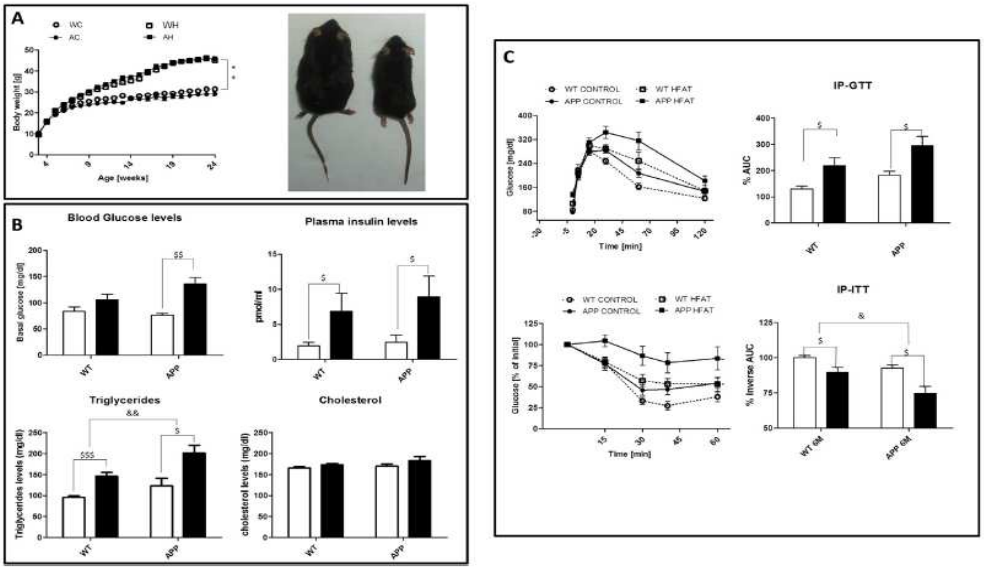

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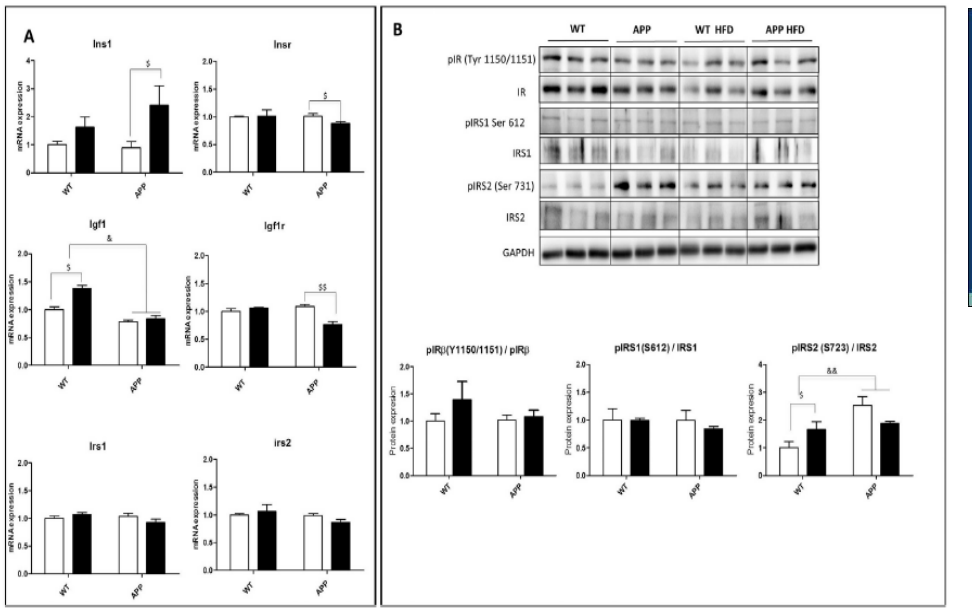

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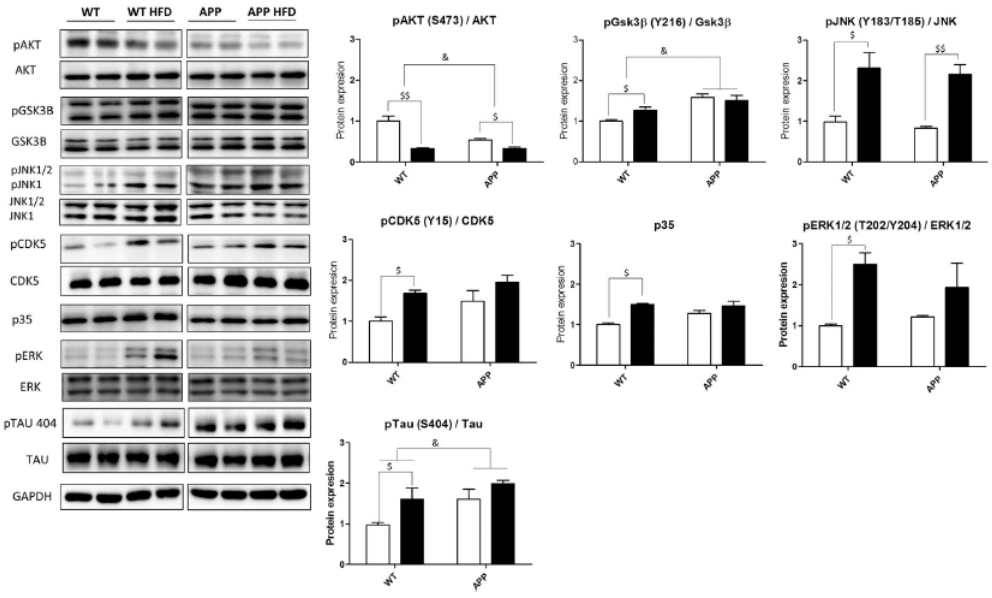

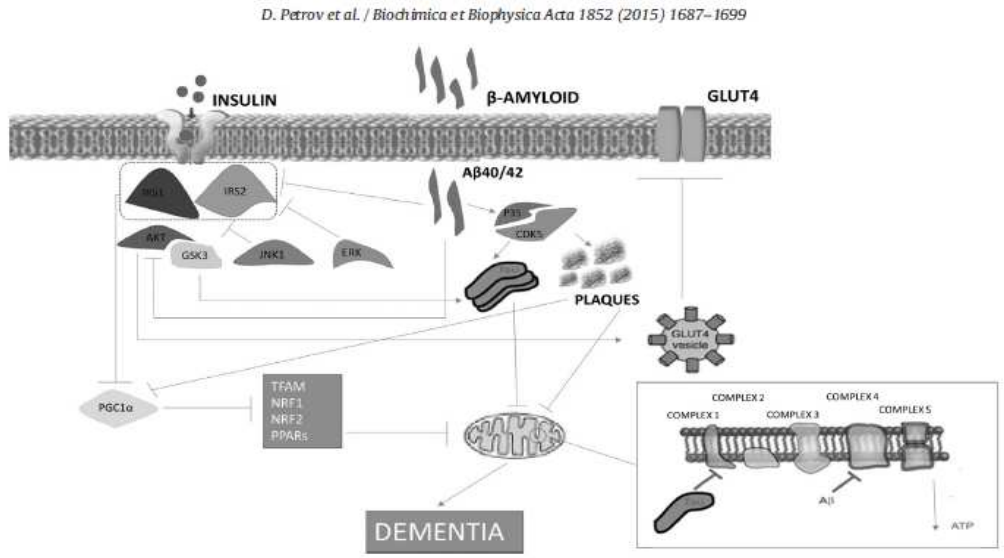

Evaluation of the Role of JNK1 in the Hippocampus in an Experimental Model of Familial Alzheimer's Disease

Dmitry Petrov[1,3] · Melani Luque[1,3] · Ignacio Pedrós[2,3] · Miren Ettcheto[1,3] · Sonia Abad[1,3] · Mercè Pallàs[1,3] · Ester Verdaguer[3,4] · Carme Auladell[3,4] · Jaume Folch[2,3] · Antoni Camins[1,3]

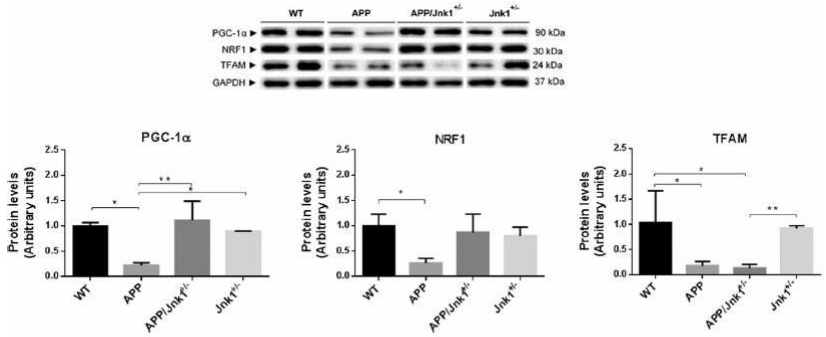

Fig. 2 a Representative immunoblot images and b quantification of key molecules involved in mitochondrial regulation in the hippocampus of 9-month-old WT, APPswe/PS1dE9, APPswe/PS1dE9/Jnk1+/−, and Jnk1+/− mice (n=4–6 independent biological replicates per group). Statistical analysis was performed with regular one-way ANOVA, with Tukey's post hoc test: *p<0.05; **p<0.01

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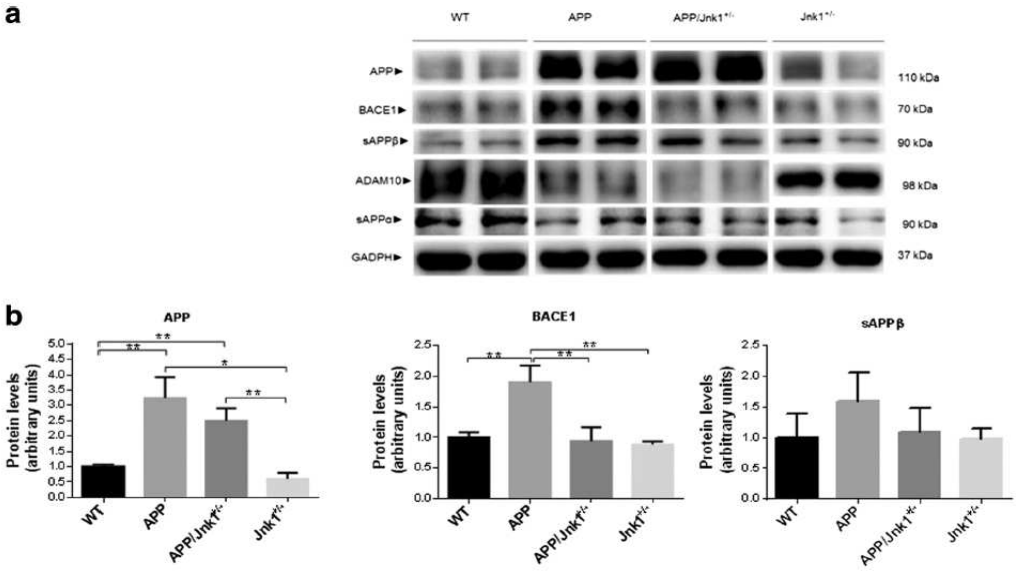


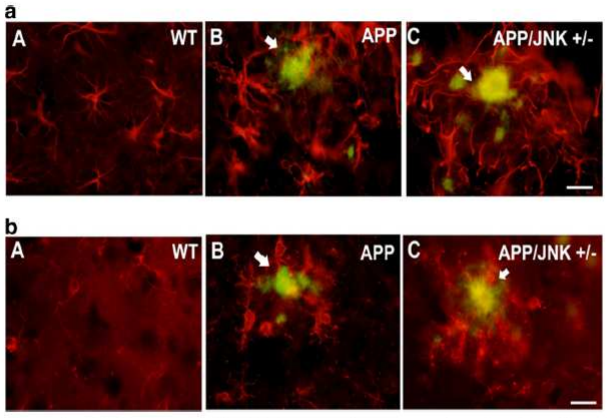
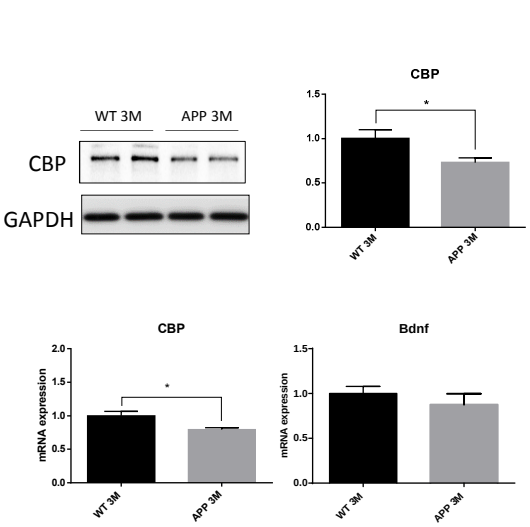
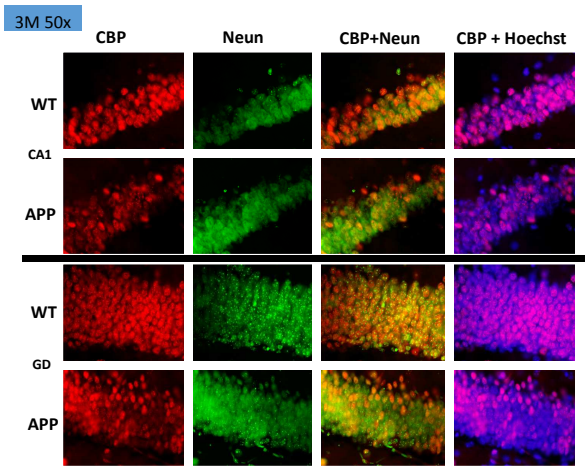
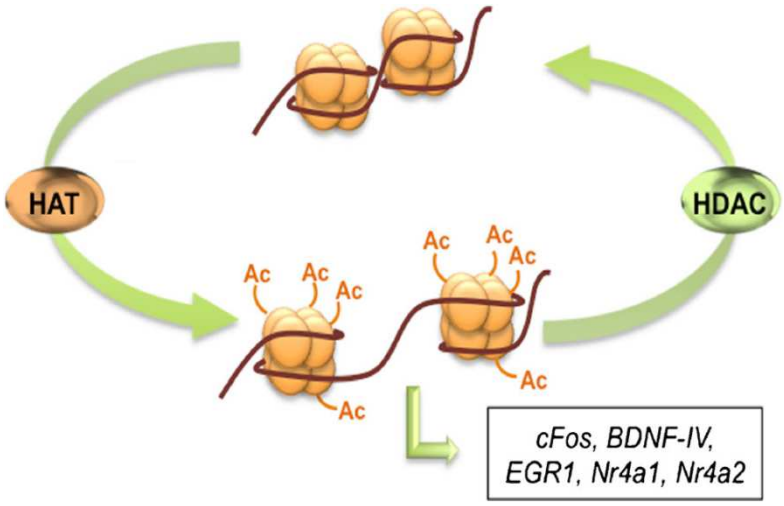
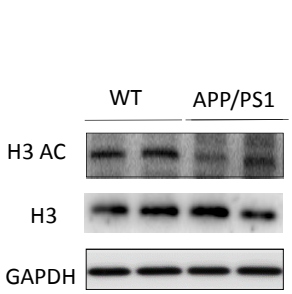


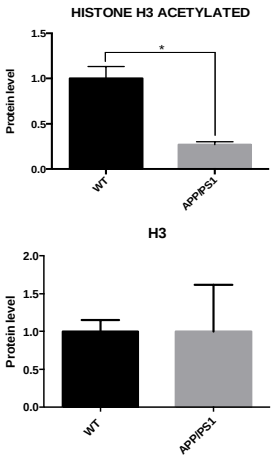
Fig. 6 **a** Immunohistochemistry against GFAP and **b** against iba-1, in 9-month-old mice. Brain sections were obtained from wild-type, transgenic APPswe/PS1dE9 mice, and heterozygote APPswe/PS1dE9/Jnk1+/− mice. **a** In wild type, the astrocytes display a non-reactive morphology (*arrows*). **b**, **c** In APPswe/PS1dE9 and APPswe/PS1dE9/*Jnk1*+/− mice, a reactive astrocytes (*arrow*) are located around β-amyloid plaques (Aβ depositions) (*arrowhead*). Double immunostaining of glial cells and plaque by thioflavin S: show amyloid plaque (in *green*) colocalized with astrocytes and microglia (GFAP and Iba 1 in *red*). *Scale bar* in (**a**–**c**) represents 100 μm

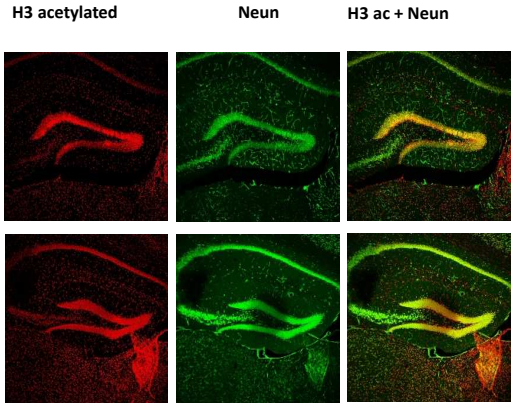

WT 3M
APP 3M
CBP
GAPDH
CBP
mRNA expression
WT 3M
APP 3M
Bdnf

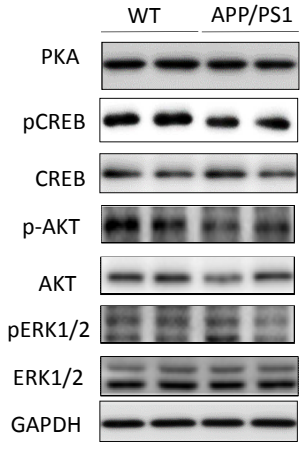

3M 50x
CBP
Neun
CBP+Neun
CBP + Hoechst
WT
CA1
APP
WT
GD
APP

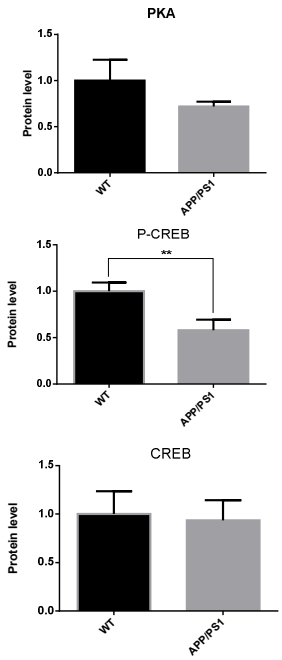

HAT
HDAC
Ac
cFos, BDNF-IV,
EGR1, Nr4a1, Nr4a2


WT
APP/PS1
H3 AC
H3
GAPDH


HISTONE H3 ACETYLATED
Protein level
1.5
1.0
0.5
0.0
*
WT
APP/PS1
H3
Protein level
2.0
1.5
1.0
0.5
0.0
WT
APP/PS1


H3 acetylated
Neun
H3 ac + Neun


WT
APP/PS1
PKA
pCREB
CREB
p-AKT
AKT
pERK1/2
ERK1/2
GAPDH


PKA
Protein level
1.5
1.0
0.5
0.0
WT
APP/PS1
P-CREB
**
Protein level
1.5
1.0
0.5
0.0
WT
APP/PS1
CREB
Protein level
1.5
1.0
0.5
0.0
WT
APP/PS1

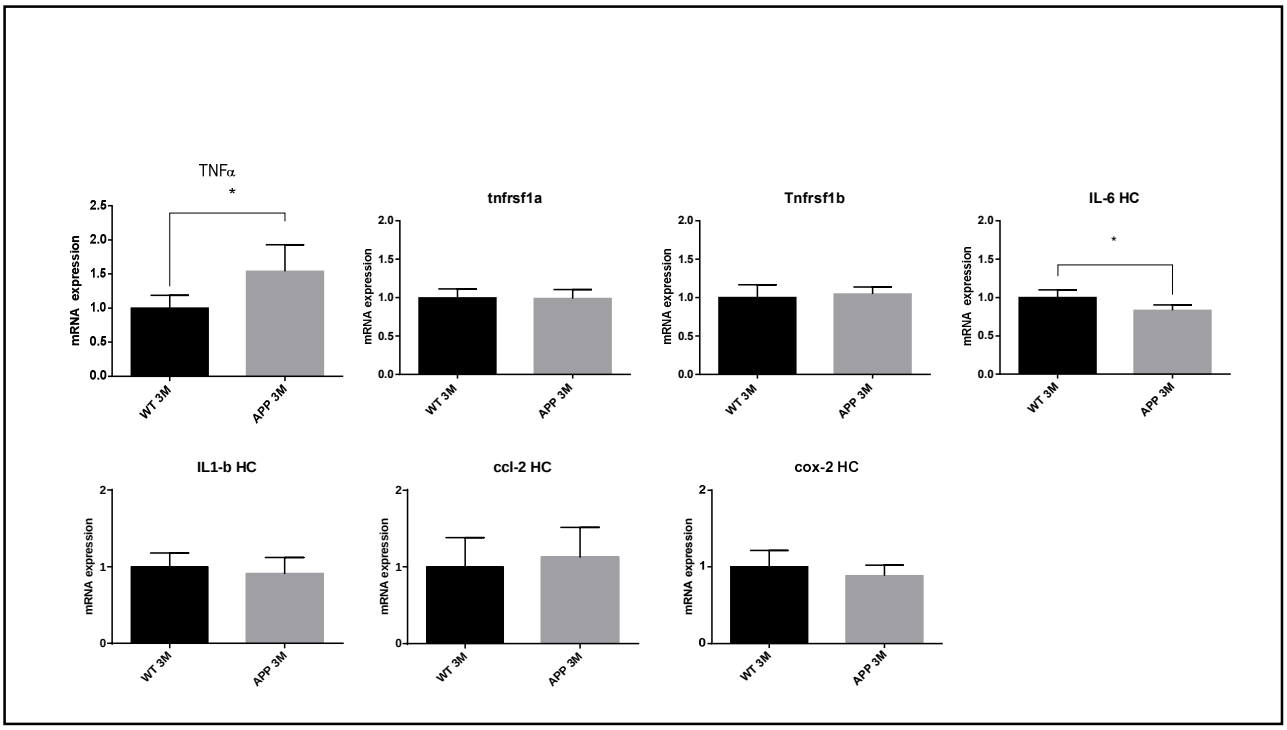


Figure 5

FALTA ESCALA!

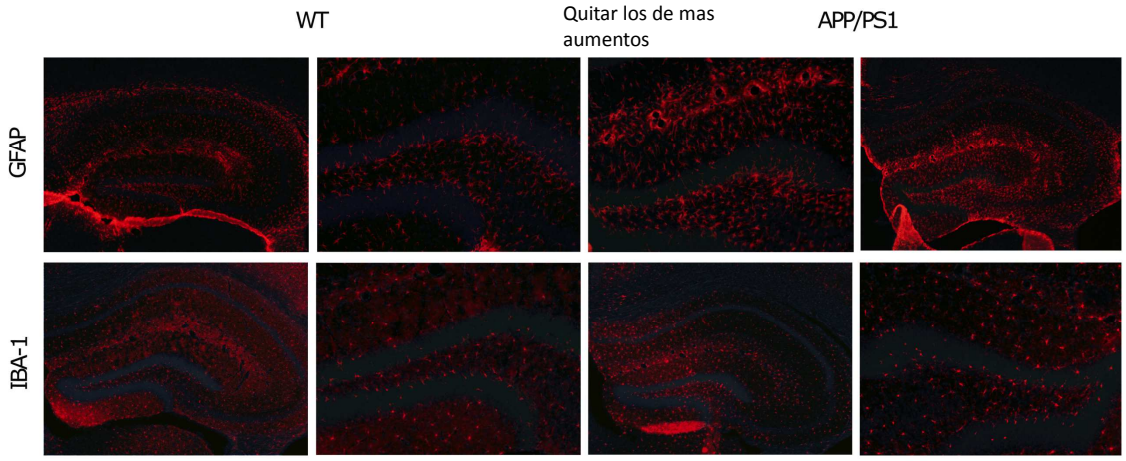
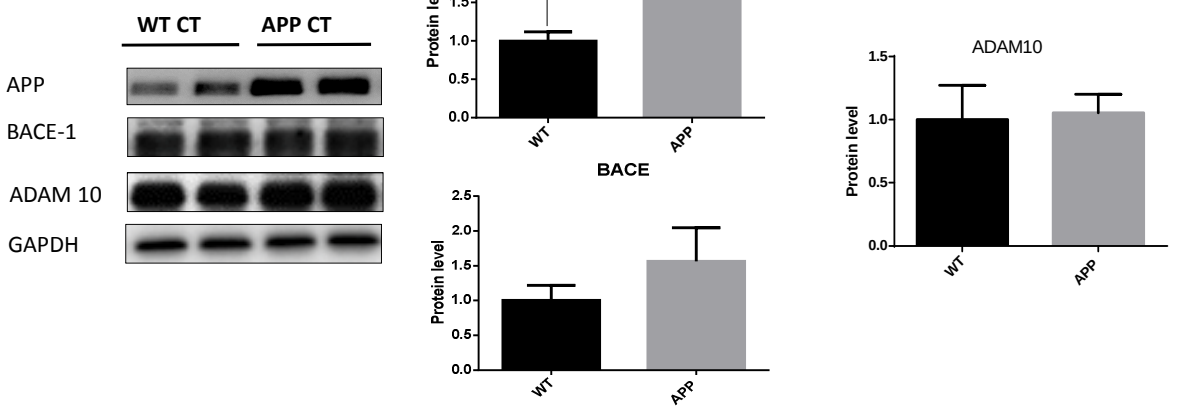
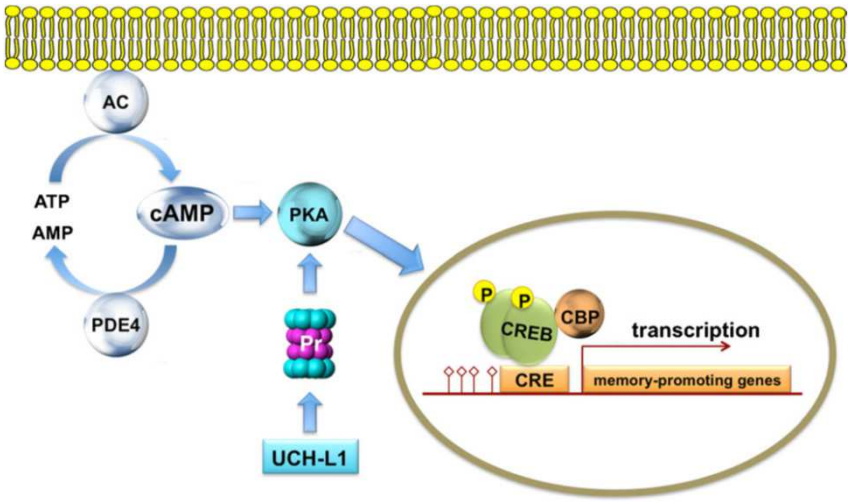


Figure 7

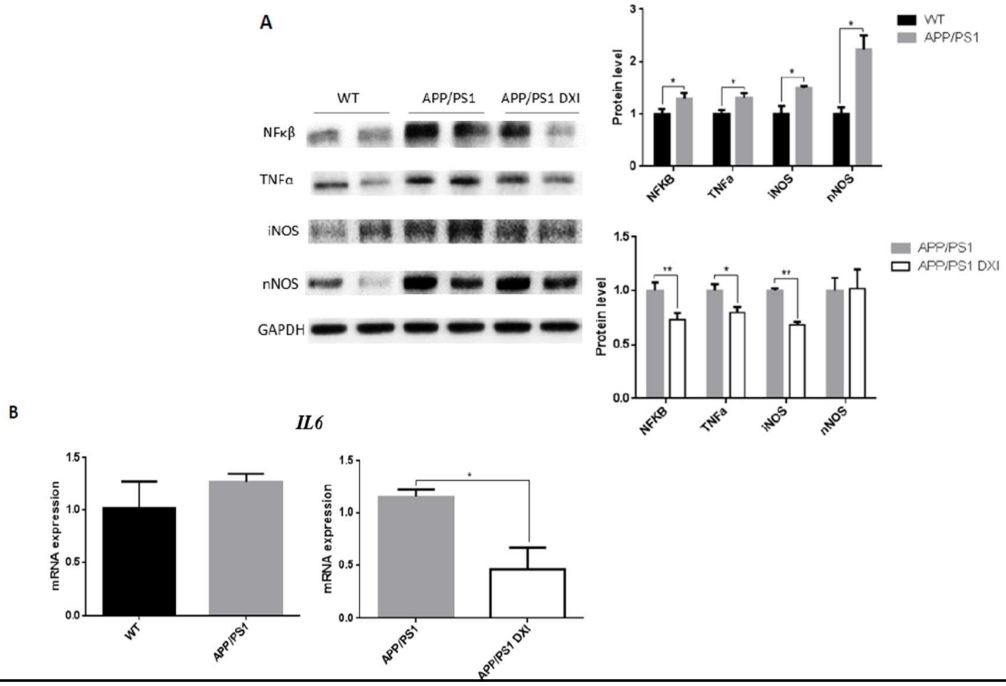

WT CT
APP CT
APP
BACE-1
ADAM 10
GAPDH

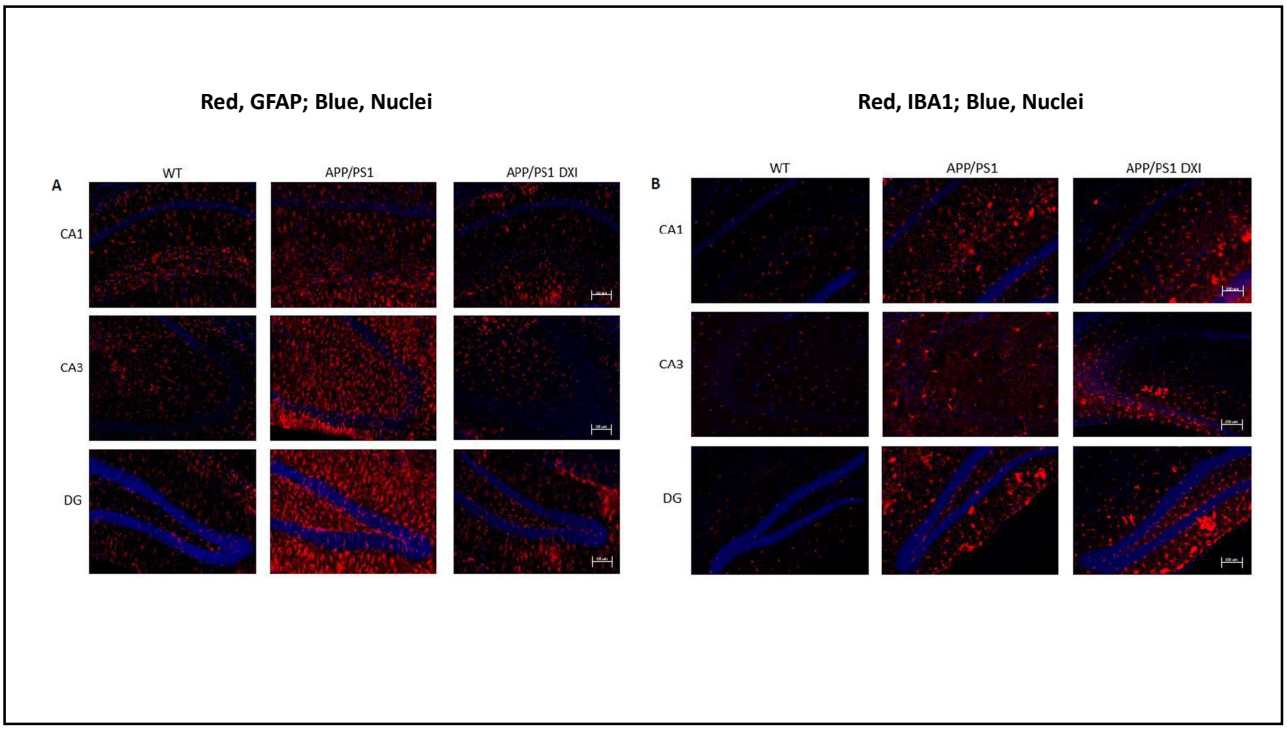
APP
**
Protein level
2.5
2.0
1.5
1.0
0.5
0.0
WT
APP
BACE
Protein level
2.5
2.0
1.5
1.0
0.5
0.0
WT
APP

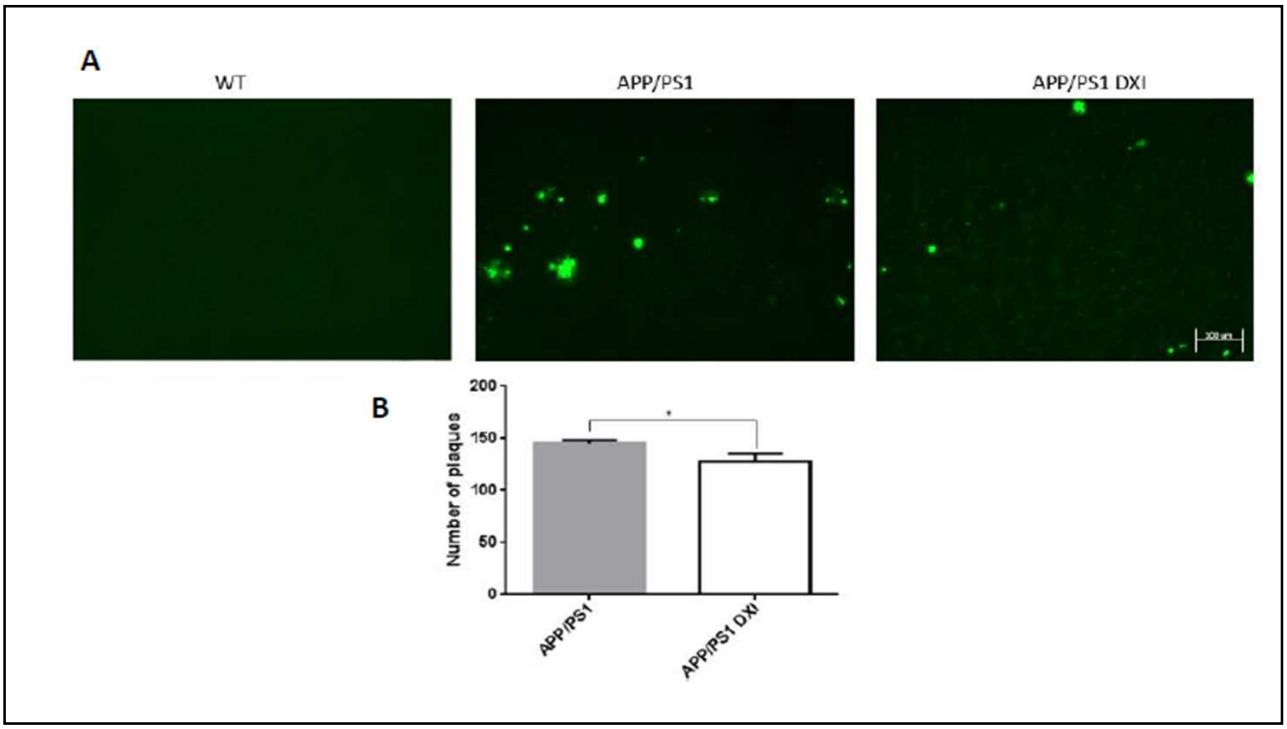
ADAM10
Protein level
1.5
1.0
0.5
0.0
WT
APP

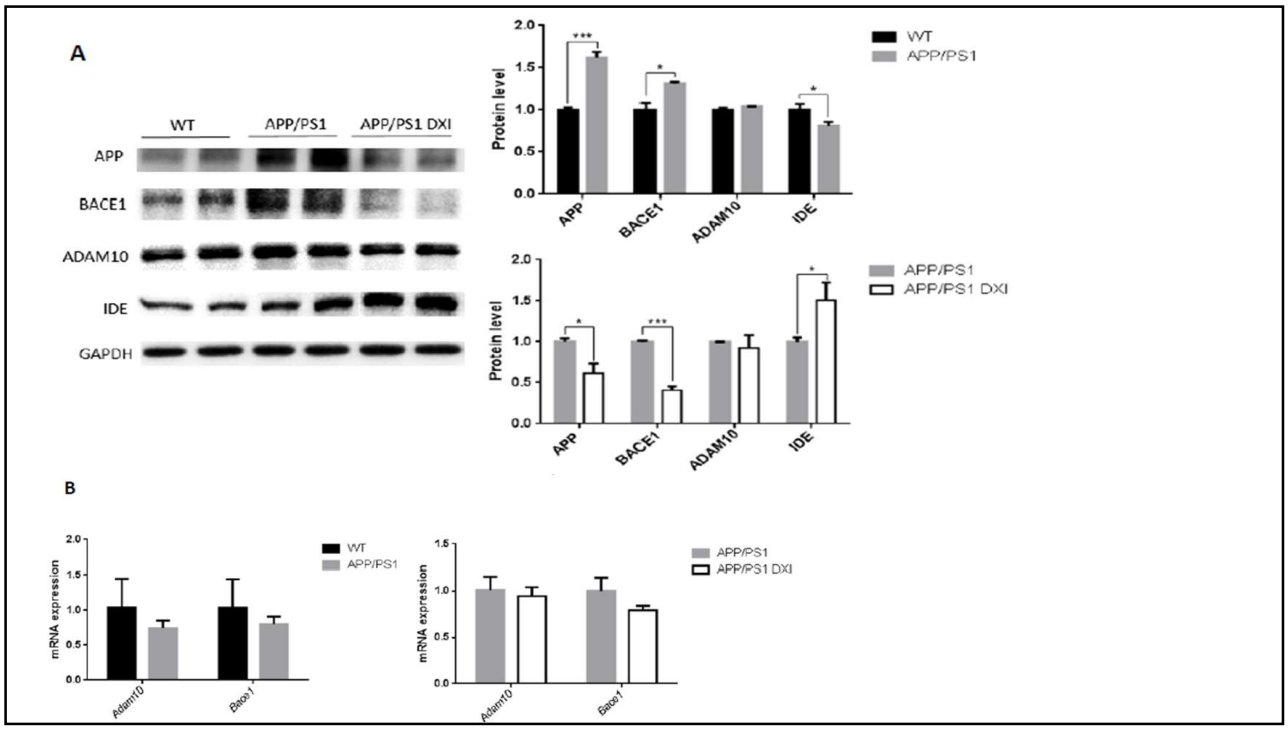

AC
ATP
AMP
cAMP
PKA
PDE4
UCH-L1
P
P
CREB
CBP
transcription
CRE
memory-promoting genes

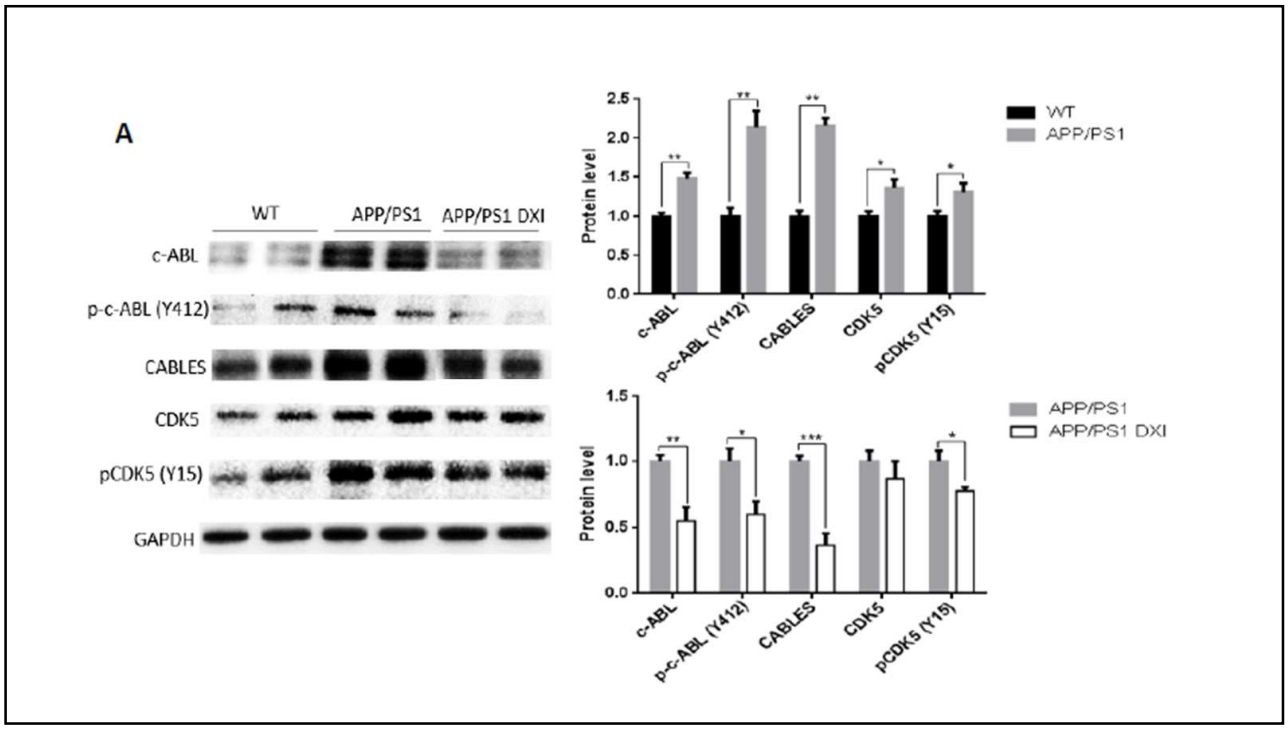
DEXIBUPROFENO

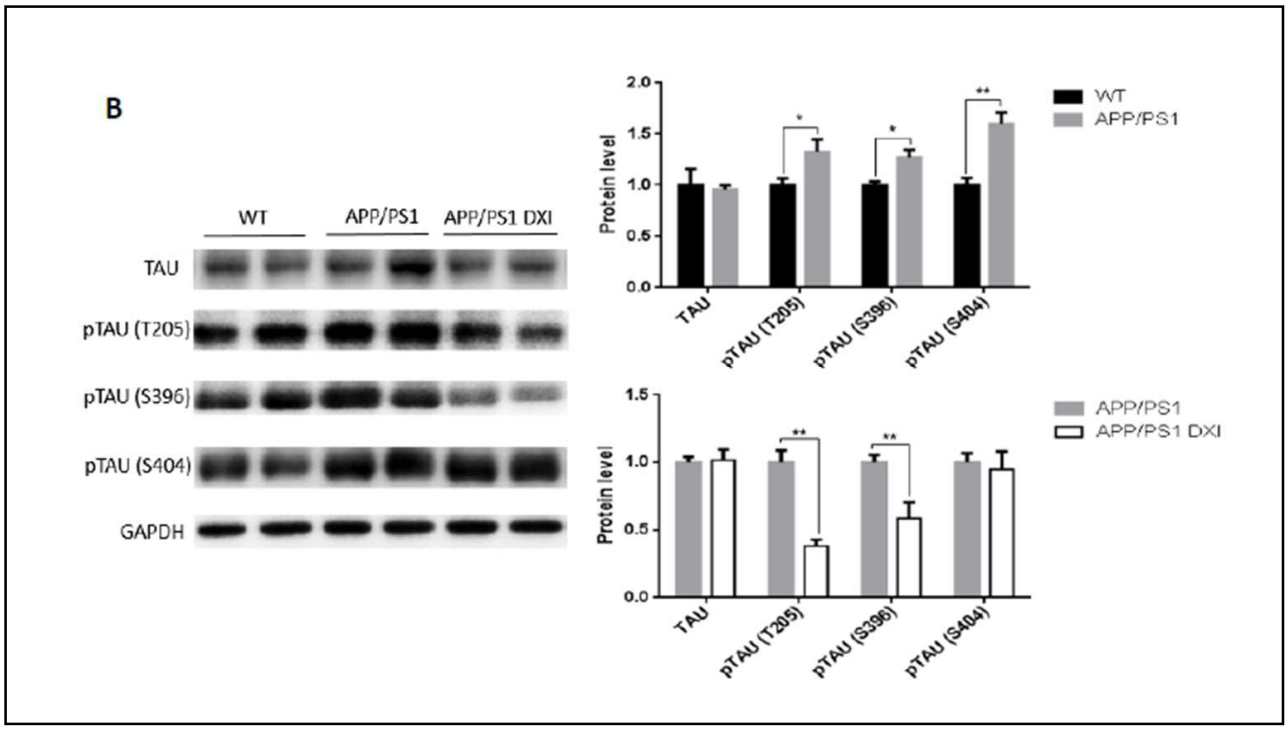


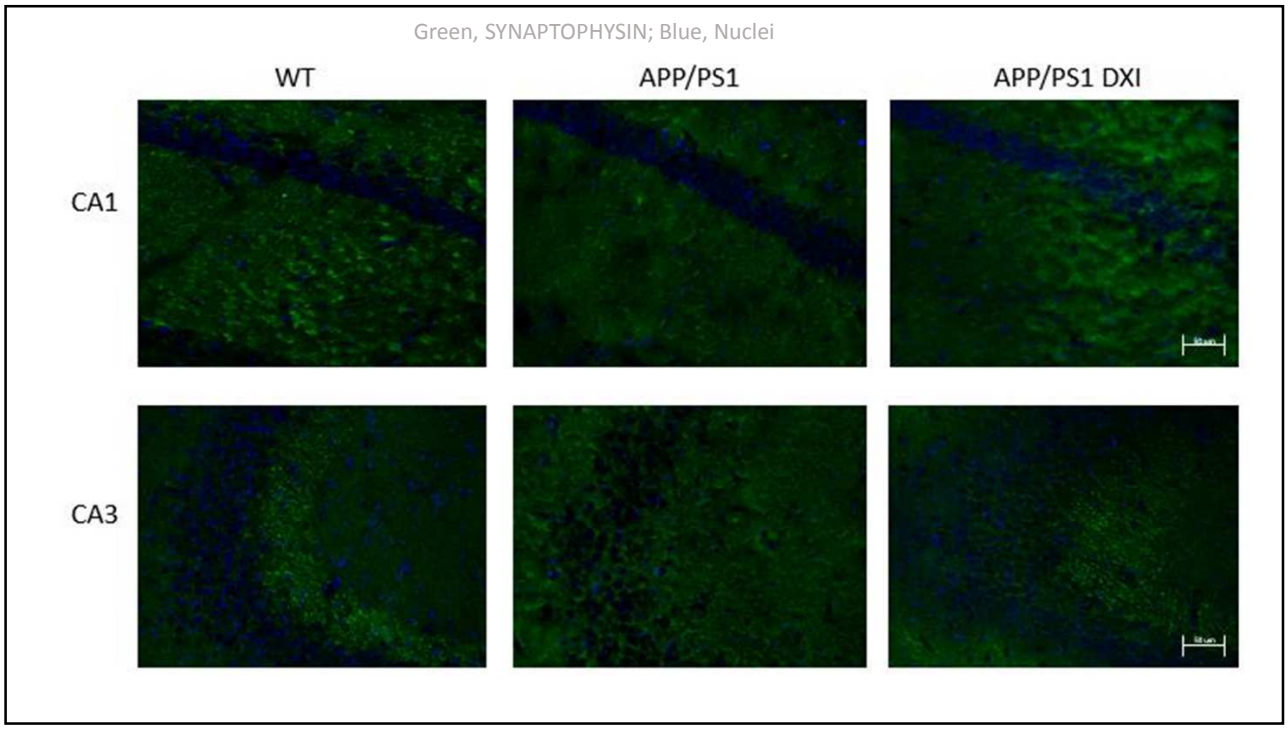

Red, GFAP; Blue, Nuclei
Red, IBA1; Blue, Nuclei
A
B
WT
APP/PS1
APP/PS1 DXI
CA1
CA3
DG

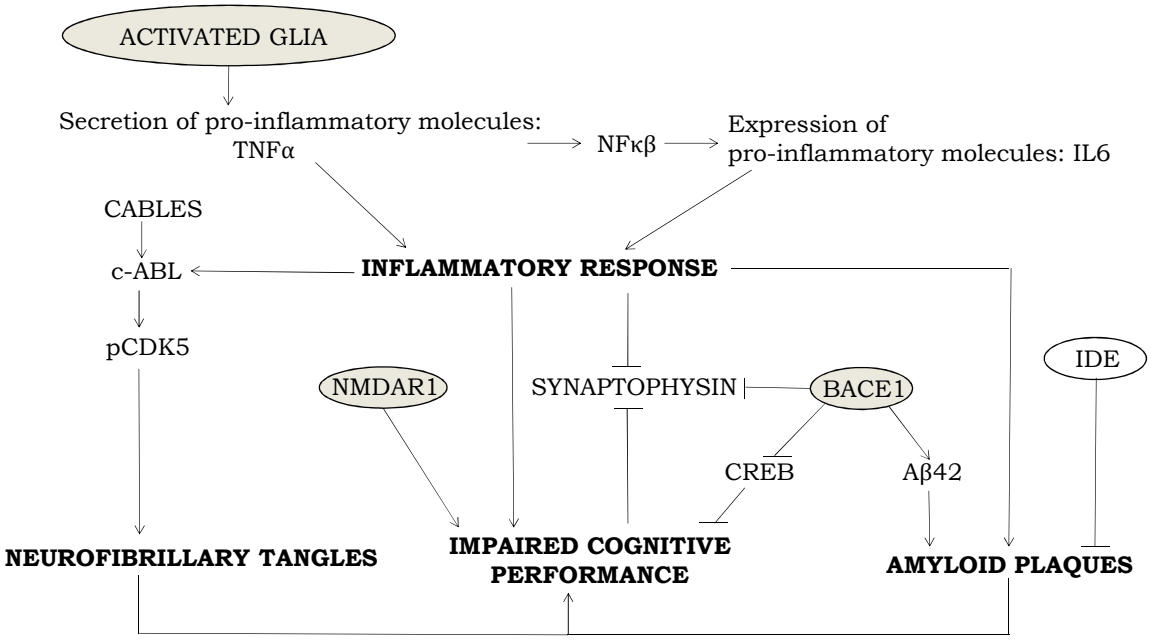

A
WT
APP/PS1
APP/PS1 DXI
B
Number of plaques
200
150
100
50
0
*
APP/PS1
APP/PS1 DXI


A
WT
APP/PS1
APP/PS1 DXI
APP
BACE1
ADAM10
IDE
GAPDH
Protein level
B
mRNA expression
Adam10
Bace1


A
WT
APP/PS1
APP/PS1 DXI
c-ABL
p-c-ABL (Y412)
CABLES
CDK5
pCDK5 (Y15)
GAPDH
Protein level

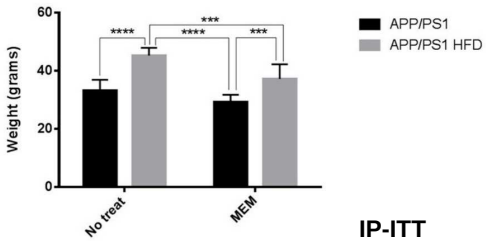

B
WT
APP/PS1
APP/PS1 DXI
TAU
pTAU (T205)
pTAU (S396)
pTAU (S404)
GAPDH
Protein level
2.0
1.5
1.0
0.5
0.0
*
*
**
WT
APP/PS1
TAU
pTAU (T205)
pTAU (S396)
pTAU (S404)
Protein level
1.5
1.0
0.5
0.0
**
**
APP/PS1
APP/PS1 DXI
TAU
pTAU (T205)
pTAU (S396)
pTAU (S404)


Green, SYNAPTOPHYSIN; Blue, Nuclei
WT
APP/PS1
APP/PS1 DXI
CA1
CA3

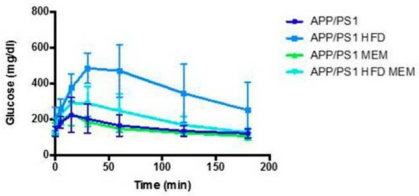

ACTIVATED GLIA
Secretion of pro-inflammatory molecules:
TNFα
NFκβ
Expression of
pro-inflammatory molecules: IL6
CABLES
c-ABL
INFLAMMATORY RESPONSE
pCDK5
NMDAR1
SYNAPTOPHYSIN
BACE1
IDE
CREB
Aβ42
NEUROFIBRILLARY TANGLES
IMPAIRED COGNITIVE
PERFORMANCE
AMYLOID PLAQUES

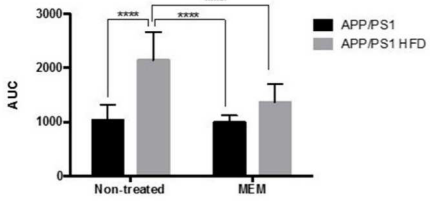
MEMANTINA

Peripheral parameters

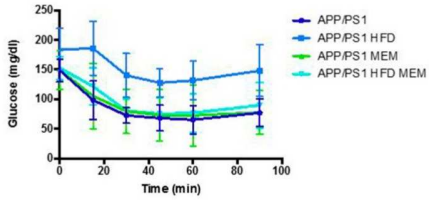


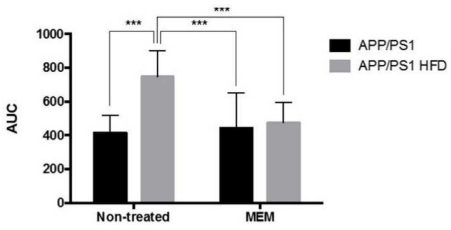
IP - GTT





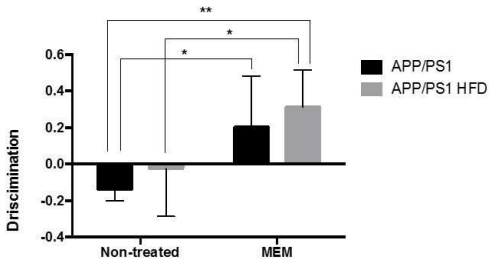
IP-ITT

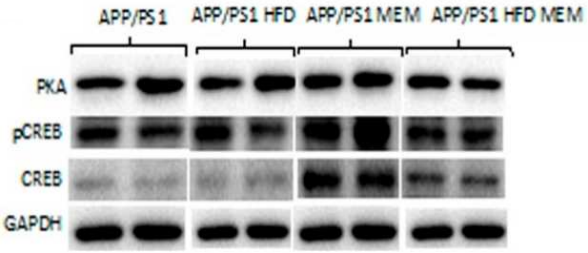


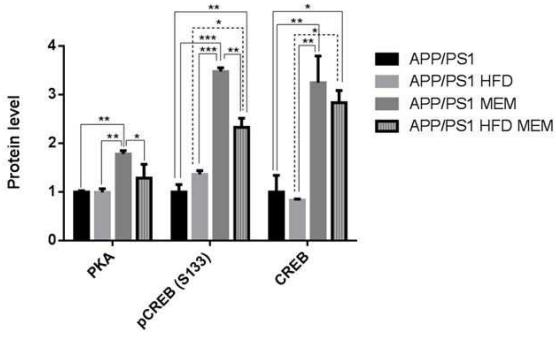


Memory improvement

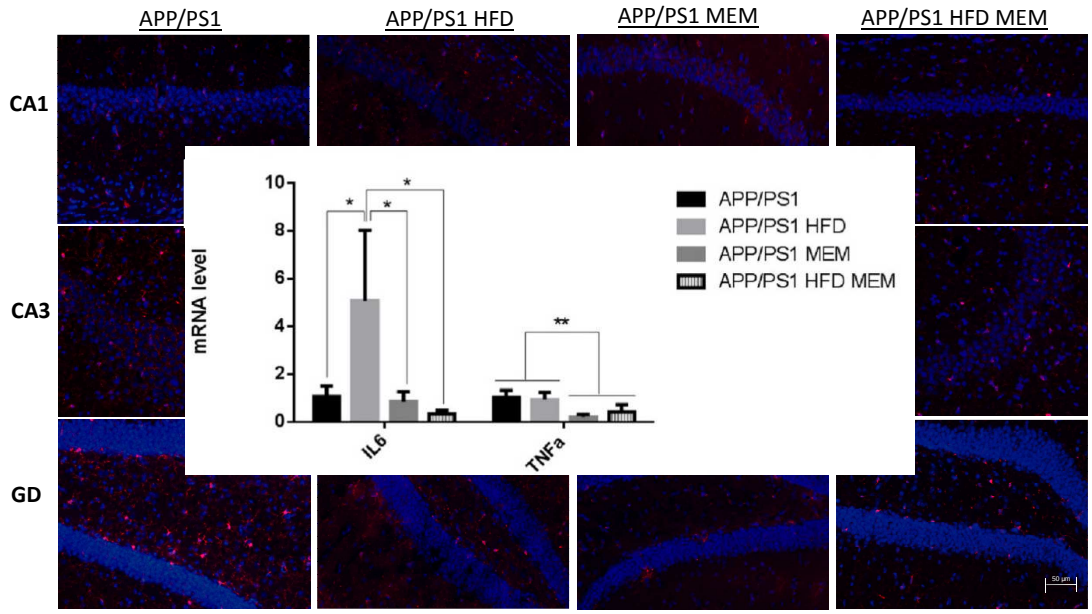
Object Novel Recognition Test





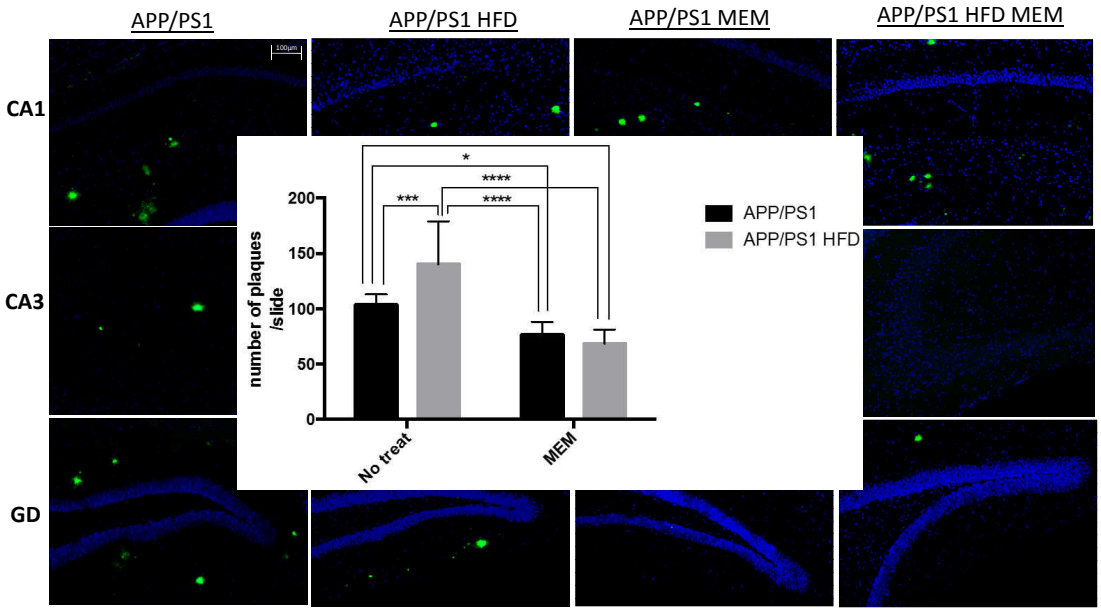


Inflammation



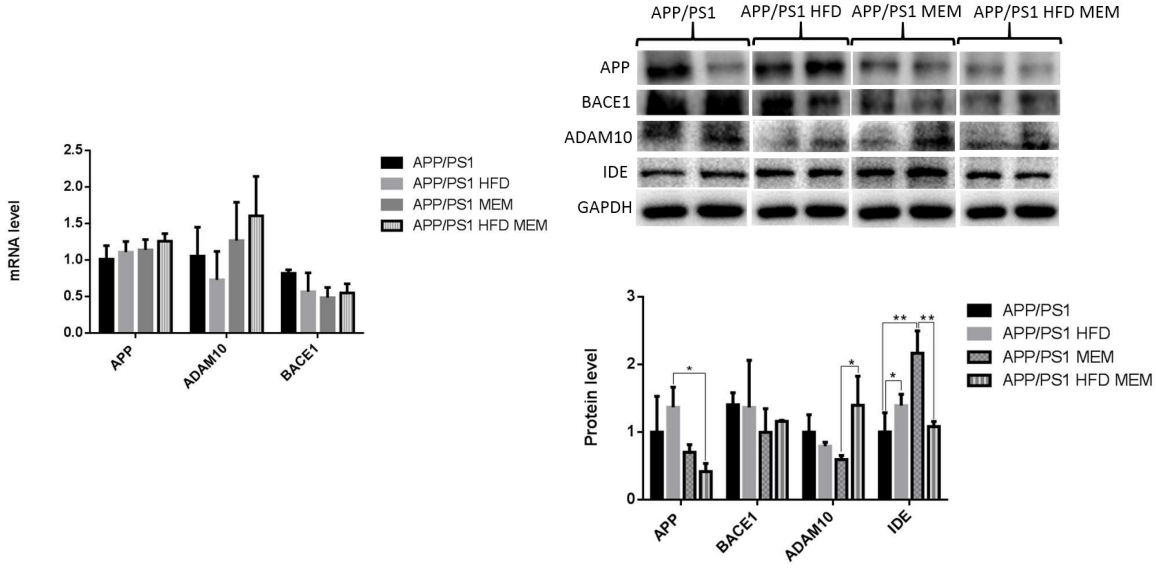
Red: IBA1. Blue: nuclei

B-amyloid plaques reduction and APP processing

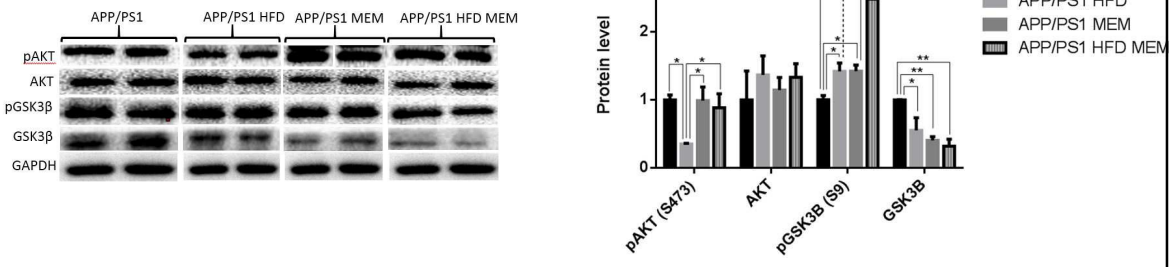


Green: amyloid plaques. Blue: nuclei

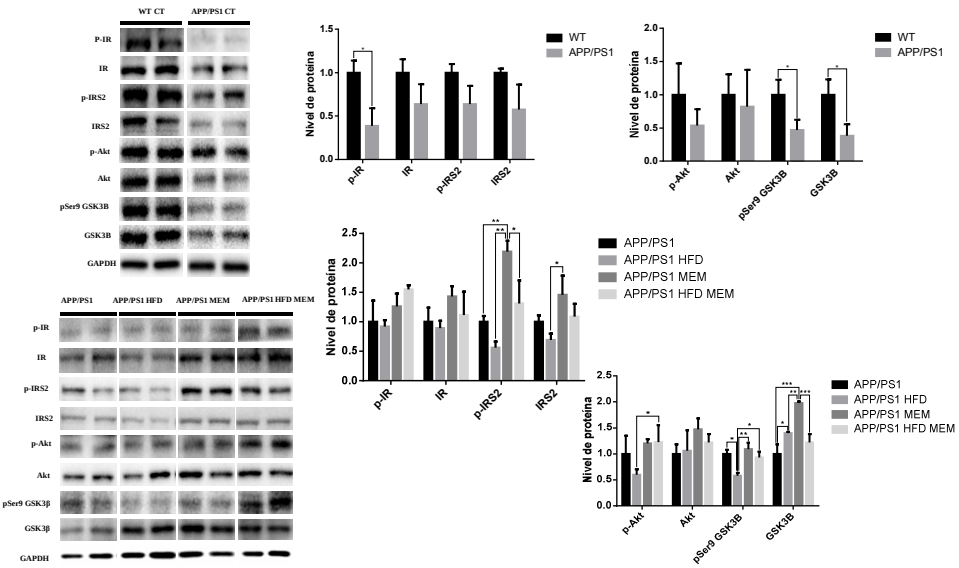
B-amyloid plaques reduction and APP processing



Insulin pathway

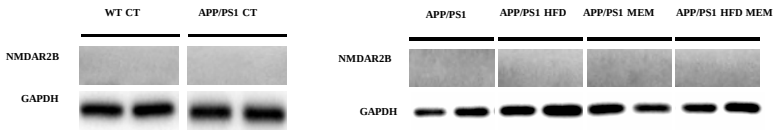


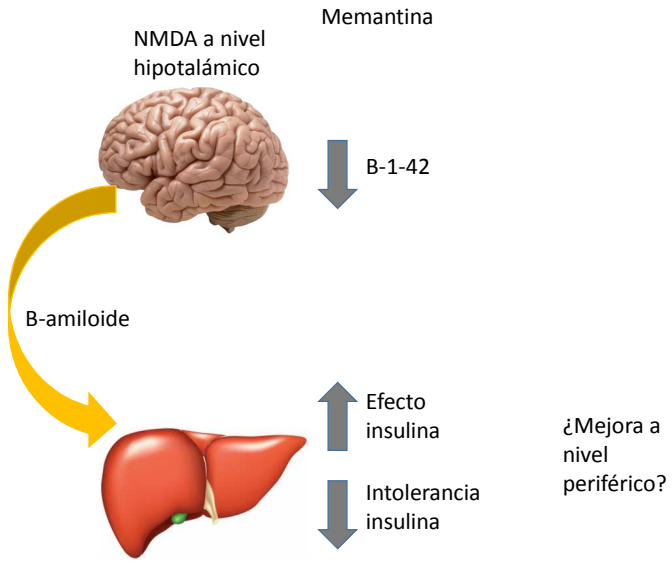
- Resistencia a la insulina



Imágenes representativas de Western Blot y cuantificación de varias proteínas relacionadas con la vía de la insulina en hígado en ratones con la cepa salvaje (WT) y la cepa transgénica (APP/PS1); y en ratones APP/PS1 no tratados Vs ratones APP/PS1 tratados con MEM de 6 meses de edad. Los valores son promedios ± Errores Estándar de la Media (SEM). Se utilizó una t de Student para comparar los grupos WT CT y APP/PS1 CT; y ANOVA de dos vías con la prueba de Tukey, los valores p< 0.05 fueron considerados estadísticamente significativos.

Receptores NMDA en el hígado





Mechanisms of Ageing and Development xxx (2016) xxx-xxx

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com

Long-term exposition to a high fat diet favors the appearance of β-amyloid depositions in the brain of C57BL/6J mice. A potential model of sporadic Alzheimer's disease

Oriol Busquets [a, b, d], Miren Ettcheto [b, d], Mercè Pallàs [b, d, e], Carlos Beas-Zarate [f], Ester Verdaguer [c, d, e], Carme Auladell [c, d, e], Jaume Folch [a, d, **], Antoni Camins [b, d, e, *]

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[b] Departament de Farmacologia, Toxicologia i Química Terapeutica, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Barcelona, Spain
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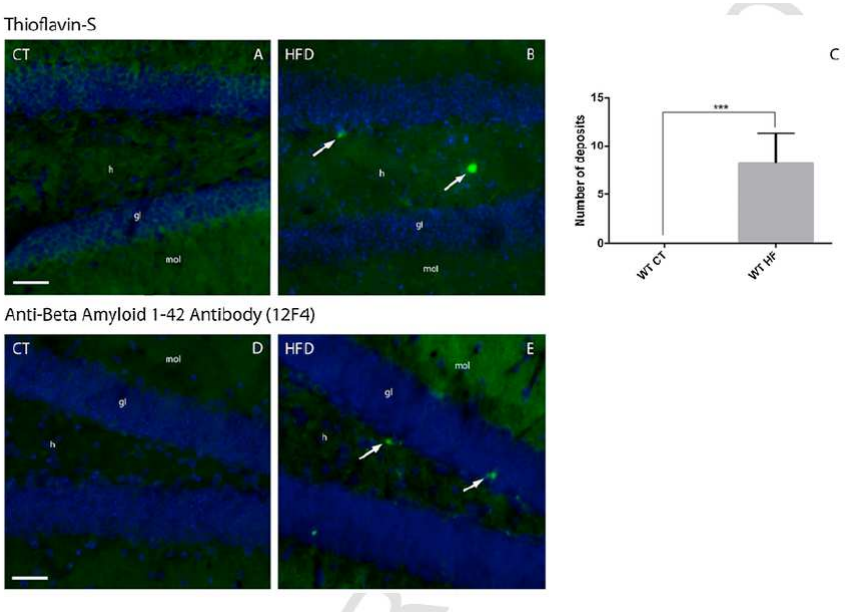


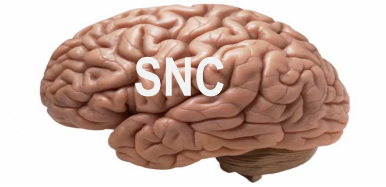
ALZHEIMER Y DIABETES

ALZHEIMER

=

TRANSTORNO METABOLICO COGNITIVO

EA: RESISTENCIA A LA INSULINA



↓ Transmisión de señal

↓ Insulina

↓ IR y IGF-1R

Resistencia a la insulina

Journal of Alzheimer's Disease 13 (2008) 323–331
IOS Press

Intranasal Insulin Administration Dose-Dependently Modulates Verbal Memory and Plasma Amyloid-β in Memory-Impaired Older Adults

Mark A. Reger[a,b], G. Stennis Watson[a,b], Pattie S. Green[a,c], Laura D. Baker[a,b], Brenna Cholerton[a,b], Mark A. Fishel[a,d], Stephen R. Plymate[a,c], Monique M. Cherrier[b], Gerard D. Schellenberg[a,c,d,e], William H. Frey II[f] and Suzanne Craft[a,b,*]

Intranasal Insulin Improves Memory in Humans: Superiority of Insulin Aspart

Christian Benedict*[,1], Manfred Hallschmid[1], Katrin Schmitz[1], Bernd Schultes[2], Frank Ratter[3], Horst L Fehm[4], Jan Born[1] and Werner Kern[4]

[1]Department of Neuroendocrinology, University of Lübeck, Lübeck, Germany; [2]Obesity Centre, Spitalregion St Gallen-Rorschach, Switzerland; [3]Novo Nordisk Germany, Mainz, Germany; [4]Department of Internal Medicine I, University of Lübeck, Lübeck, Germany

Intranasal Delivery to the Central Nervous System: Mechanisms and Experimental Considerations

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ENSAYOS CLÍNICOS

- Relación Alzheimer-Diabetes
  - Insulina
  - Pioglitazone

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ALTERACIONES METABÓLICAS

- **Señalización de la insulina (SNC)**
  - Receptor de la Insulina (IR)
  - Altos niveles de insulina
  - Multitud de funciones fisiológicas
    - Ingesta
    - Modulación de la fosforilación de tau
    - Metabolismo β-Amiloide
    - Supervivencia neuronal
    - Protección contra el estrés oxidativo

ENSAYOS CLÍNICOS

- **Insulina Nasal: Piloto**

Participantes: Enfermos de Alzheimer leve o moderado N=104 Durante 4 meses (placebo, 20 IU o 40 IU)

Resultados:

- Mejora de la Memoria "retardada" (delayed)
- Mejoras en la cognición (diferentes test)
- Sin diferencias significativas en los biomarcadores del fluido cerebroespinal. (pTau i β-Amiloide)

- **Insulina Nasal: Fase 3**

Participantes: Enfermos leves de Alzheimer N=240 Durante 12 meses (placebo, 40 UI)